UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE, S.A. and ROCHE PALO ALTO, LLC,

Plaintiffs,

-vs-

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.

Defendants.

CIVIL ACTION NUMBER:

11-3962

TRIAL

REDACTED VERSION

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
June 15, 2015

B E F O R E: THE HONORABLE MARY L. COOPER
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C., Section 753

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/S/ Carol Farrell, CCR, CRR, RMR, CCP, RPR, RSA

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I N D E X

(In open court. June 15, 2015, 9:30 a.m.)

THE COURT: Good morning, everyone.

ALL: Good morning, your Honor.

THE COURT: How is everybody today?

ALL: Good.

THE COURT: Okay. What would you like to start with this morning?

MR. ASHKENAZI: Your Honor, we're planning on playing some deposition designations this morning.

THE COURT: All right. Is there any dispute about them, these?

MR. ASHKENAZI: Not that I'm aware of.

MR. SENDER: Other than the sort of the standing 403 objection to our experts who did not appear, you know, we've designated what we could out of it to try to provide some context.

THE COURT: All right. Well, I'll see them, and I'll rule at some point. But we'll definitely know what we're delineating as your objection.

MR. SENDER: Thank you, your Honor.

MR. LIZZA: Your Honor, in that regard as requested by your Honor for the line-by-line analysis, we've prepared a chart with the designations and with our basis for relevance and probative value. So if I may approach, I can hand that chart up.

THE COURT: Sure. Have you served it?

MR. SENDER: No, they have not, your Honor.

MR. LIZZA: We're serving it now.

THE COURT: Okay. And, again, you don't need to respond until you've had a chance to digest it and me, too. Okay? Fine.

MR. ASHKENAZI: Your Honor, at this time, we'd like to play the deposition designation of Dr. Maurie Markman who is DRL's expert clinical oncologist. According to DRL, Dr. Markman is the president of medicine and science at Cancer Treatment Centers of America. Dr. Markman has more than 20 years of experience in cancer treatment. He has held clinical, research, teaching and management positions in several highly regarded medical institutions in the U.S.

Dr. Markman has extensive experience with all the 5-HT_3 receptor antagonist drugs approved in the U.S. Dr. Markman was deposed regarding his expert opinions in this case.

And for the record, your Honor, we have a binder with the corresponding deposition exhibits. Markman Deposition Exhibit 1 corresponds to DTX-1206.

THE COURT: I'm sorry. Just a second, please. I'll tell you when I'm ready.

MR. ASHKENAZI: Okay.

THE COURT: Was he deposed once or twice?

MR. ASHKENAZI: Once, your Honor.

THE COURT: Okay. I'm just reviewing what you've already told me.

What is this institution where he practices? President of medicine and science at the organization called Cancer Treatment Centers of America. This is a whole consortium of hospitals? Where does he practice?

MR. ASHKENAZI: Your Honor, that was the description provided to us about Dr. Markman. He's DRL's expert. I guess I would defer to them on what that institution is.

THE COURT: All right. Never mind.

Thank you. So, what were you saying?

MR. ASHKENAZI: Just providing for the record which DTXs correspond to the deposition exhibits identified during the video.

So, Markman Deposition Exhibit 1 corresponds to DTX-1206. And, your Honor, this is in the binder under tabs. Markman Deposition Exhibit 1, Exhibit I is DTX-283. Markman Deposition Exhibit 4 is PTX-398, and Markman Deposition Exhibit 11 is PTX-297.

THE COURT: Okay. Will you be showing on the screen these exhibits, or is that going to be too cumbersome?

MR. ASHKENAZI: I believe we will be showing them on the screen, your Honor.

THE COURT: Okay.

MR. ASHKENAZI: Thank you.

THE COURT: Fine. And about how long is this video?

MR. ASHKENAZI: This one is 23 minutes, your Honor.

THE COURT: Okay. Fine.

(The video deposition of Maurie Markman was played as follows:)

Q. Dr. Markman, good morning.

A. Good morning.

Q. Let's take a look at your opening report, Exhibit 1, specifically Paragraph 4. It states here that you were asked by counsel for DRL to provide expert opinions on certain issues related to the clinical aspects of the asserted claims of the '219 patent, correct?

A. That's correct.

Q. Can you tell me generally what your experience is with respect to palonosetron, perhaps starting with any use of palonosetron you have in your clinics?

A. Well, it's a drug that I've used, you know, extensively since the day it was -- came on the market. I can't tell you, you know, the number of times. I treat patients with gynecological malignancies, that's my clinical expertise, and we use a lot of platinum, which is not only the drug that gave chemotherapy its bad name 20, 30 years ago, but it's also the drug that is the one -- from the point of view of nausea and vomiting, but it's also the drug that -- where -- the class of drugs where we have most use for serotonin antagonists.

So, I've used all of the serotonin antagonists, and this is -- obviously a wonderful product and used it -- I've used it extensively.

Q. Can you elaborate on what it is about Aloxi® that you think makes it a wonderful product?

A. Well, I -- you know, I think it's a -- you know, serotonin antagonists have been around for a long time. And they were -- when they first came into existence now many, many years ago, they changed the way we thought about the management of chemotherapy-induced emesis.

What Aloxi® -- I'll say Aloxi®, it's easier, shorter, the benefit of that drug was that it had a very important effect on -- we divide nausea and vomiting in chemotherapy at least with a highly emetogenic chemotherapy, like platinum, into what we call acute, and then we call it delayed emesis. And -- and what had been very well recognized is that the serotonin antagonists were quite effective and the -- that is, the first generation, again, I -- when I use the term "first generation," to be.

THE COURT: Just a second, I'm sorry. There's a transcription error back there, and I wouldn't want the court reporter here to not be informed about that transcription error in the dep.

If you'll just scroll back a moment. And I'm not going to pick up every one, but if I think that it's worth noting, I

will.

A. That drug was that it had a very important effect on -- we divide nausea and vomiting in chemotherapy at least with a highly emetogenic chemotherapy, like platinum, into what we call acute and we call delayed emesis.

THE COURT: Okay. Stop it. You see that word, "but" that he's about to reach? What he actually says is "what had been." "What had been very well recognized." I think you'll agree with me when you hear it.

THE WITNESS: Very well recognized --

THE COURT: Back it up. We missed it.

THE WITNESS: -- shorter, the benefit of that drug was that it had a very important effect on -- we divide nausea and vomiting in chemotherapy at least with a highly emetogenic chemotherapy, like platinum, into what we call acute and we call delayed emesis. And what had been very well recognized is that the serotonin antagonists were quite effective in the -- that is, the first --

THE COURT: "In the." "In the" not "and the."

THE WITNESS: But I'll use the term "first generation" to be ondansetron, granisetron were very effective in the acute nausea and prevention of acute nausea and vomiting, not perfect, but certainly a lot better than the existing standards at that time when they came on existence. But they were not very effective in delayed nausea and

vomiting, and Aloxi® was the first drug of that category or actually any category that was effective both for acute and delayed. And, so, nausea and vomiting induced by highly emetogenic chemotherapy. So, with the introduction of this drug, it became, you know, widely utilized by oncologists, including me.

Q. So, just to make sure I have that, you mentioned that the Aloxi® was the first drug approved for delayed emesis in connection with highly emetogenic chemotherapy?

A. Well, the one thing I want to -- I mean, you know, I'm not 100 percent sure about who approved what, when or things like that, I'll tell you. From my perspective at a clinical level, their registration strategies and things get approved, but at a clinical level I think what I said is certainly correct, and it may actually registration true, too, I'm not -- I'm speaking at the clinical level.

Q. Would you agree that one of the benefits of Aloxi® versus the first generation of 5-HT_3s was its ability to treat delayed emesis associated with CINV generally?

A. Yes.

Q. So, you mentioned that you continue today to prescribe Aloxi®; is that correct?

A. Absolutely.

Q. And you started prescribing Aloxi® when it was first approved back in 2003?

A. If that was the date, yes.
Q. Not to be a memory test.
Have -- over the course of the last roughly, say, decade that you've been prescribing Aloxi®, have your -- the frequency of your prescriptions with respect to Aloxi® changed at all during that time period?
A. I would say I don't -- I don't think so.
Q. Do you prescribe other antiemetics in connection with your practice?
A. I do. And I would certainly -- I think it's appropriate to add when you go back to your previous question and, I'm sorry, I should have answered you know some of the determinations are made today by a contracting issues and, you know, this is a market, there are other opportunities and there are other approaches towards management of acute and delayed emesis. And, so, some of those decisions are actually made, I don't want to say at a higher level than me, but a different level than me.
Q. For example, I would imagine that given the presence of -- or the availability of generic 5-HT_3s that at times I would assume you prescribed generic?
A. Well, I would say that's certainly one approach. And the other approach is, of course, there are the use of generics and the other categories of drugs that could prevent delayed emesis, specifically Emend, for example.

Q. NK-1 receptor antagonists?
A. Right.
Q. So, I'm asking about that POSA standard you've applied, this hypothetical person, would that hypothetical POSA, in deciding what drug molecule to pursue for development, take into account the sort of market considerations we have been discussing?
A. I believe so.
Q. Do you have an opinion as yes or no what standards you applied in this case whether a POSA would take those generic competition and number of competitor products into account in deciding whether to pursue a drug product or not?
A. I believe they probably would, yes.
Q. So, we've done a little bit of this already, so I'll try not to be duplicative, but I want to talk about the state of the art in antiemetics in 2002.

So, that's the time period that's relevant to your opinions in this case. Roughly 2002, 2003, correct?
A. Correct.
Q. So, is it correct that in this time period you were obviously a practicing clinician, correct?
A. Correct.
Q. And I assume that you studied the literature and remained up to date on developments in the field at that time?
A. That's correct.

Q. You were comfortable providing opinions about what the state of the art at that time was, correct?
A. That's correct.
Q. And did you stay up to date on potential new therapies under development in the antiemetic field?
A. Um, yes.
Q. And did that include potential new therapies that would treat CINV, for example?
A. That's correct.
Q. And I think you said this before, but, please, I don't want to put words in your mouth, so correct me if I'm wrong, but I think you essentially said that the 5-HT_3 antagonists that were available in 2002 weren't -- weren't -- weren't satisfactory in terms of treating delayed CINV; is that correct?
A. I believe that was the -- it would be a fair statement of my opinion, as well as that of what the clinical community would -- would say, as well.
Q. Was it also true in 2002 that the available setrons were comparable in effectiveness and toxicity?
A. The serotonin antagonist inhibitors, yes.
Q. Then available?
A. Yes.
Q. Would you also agree that in the 2002 time period, chemotherapy-induced emesis was extremely difficult to

control?

A. Well, you know, again, it's a -- it -- your -- it's a little hard to answer that question. I mean, you could say today we're not perfect either. I think we -- what -- what happened with the availability of the serotonin antagonists, there was a tremendous improvement, and certainly with the acute nausea and vomiting, and it became the delayed that was a greater concern, but even then we still had a, as we do now, still a percentage of patients where at least they would say the therapies are not as good as we'd like them to do.

So, it's a -- I think it's a relative answer. I would certainly have said then, and I'll say now, we're not perfect. We have gotten better, but, you know, if you look at 2002, 2003 compared to ten years earlier before the availability of the serotonin antagonists, we were much better. It's you know, again, it is all relative.

Q. It would be helpful if you could get Tab 7. It's very convenient in fact that you wrote a paper in 2002 that I think touches upon a lot of this, so it is very convenient.

A. Thank you.

Q. Do you recognize this document, Exhibit 4?

A. Well, yes.

Q. Can you tell me what it is?

A. It's a review article I wrote for the Cleveland Clinic Journal of Medicine when I was at that institution in 2002.

Q. And does it sort of generally summarize the paper is discussing essentially the state of the art in the treatment of CINV in the 2002 time period?
A. I haven't looked at this for a long time, but I -- I certainly would have every reason to believe that that is exactly what this paper does.
Q. Okay. So, for example, on the first page, we were just talking about on the right side column, it's about midway down the page you see there's a sentence that starts, "Given the complexity of"...
A. Yes.
Q. All right. If you could just -- well, I'll read it into is the record. "Given the complexity of the emetic process and the multiple neuroreceptors involved, chemotherapy-induced emesis has been extremely difficult to control completely."
Do you see that?
A. Yes.
Q. And do you agree that that was consistent with the state of the art in 2002 concerning antiemetics?
A. Yes.
Q. All right. You state here, "For example, an antiemetic agent that completely inhibits a specific neuroreceptor involved in emesis may activate another receptor that leads to nausea and vomiting by an alternative pathway," correct?
A. Yes.

Q. Do you agree with that statement, as well, in terms of the state of the art in antiemetics in 2002?
A. Yes.
Q. And the paragraph continues, "Furthermore, although the neurophysiology of acute emesis is fairly well characterized, our understanding is extremely limited of the pathways involved with either delayed or anticipatory nausea and vomiting."
Do you see that?
A. Yes.
Q. Is that also in your opinion an accurate view of the state of the art of antiemetics in 2002?
A. Yes.
Q. If you can turn next to Page 612. And I'm interested in the text that is underneath the heading delayed emesis. Do you see that, the left side?
A. Yes.
Q. It states, "Unfortunately, the pathophysiology and neuropharmacology of delayed emesis are poorly understood."
Do you see that?
A. Yes.
Q. And do you agree that also accurately reflects the state of the art of antiemetics in 2002?
A. Yes.
Q. Is it correct that it was known in 2002 that the

pathophysiologic processes of delayed and acute emesis differed?

A. Well, what we knew is that if a patient had, you know, very good control or fairly good control, it didn't --

THE COURT: All right. Let's back it up to where he begins his answer. This word "pathophysiology" is kind of a new one.

Q. Is it correct it was known in 2002 that the pathophysiologic processes of delayed and acute emesis differed?

A. Well, what we knew is that if a patient had, you know, very good control or fairly good control, it didn't -- of acute, it didn't -- it didn't necessarily translate into a control of delayed. That's what we knew.

Q. So, you knew the mechanisms between acute and delayed were different?

A. Well, again, we -- what we knew is was the clinical outcome was different, and --

Q. Okay.

A. And whether, you know, this was the entirely different process or somehow we weren't adequately controlling the acute process, again, we -- we didn't know the mechanism, still don't know the mechanism. We have hypotheses of the mechanisms and we have much better therapies, but, certainly, at a clinical level, control of the acute does not translate

into the -- necessarily into the control of the chronic -- or the delayed, not the chronic, the delayed. Delayed.

Q. What I'm trying to drill down on is that in this time period, the mechanism for what caused delayed emesis was unknown, although there were hypotheses, correct?

A. That is correct.

Q. And at the time, it was difficult to control delayed CINV, correct, with the available medications?

A. That is correct.

Q. So, if a company approached you with a new 5-HT_3 molecule and said we believe this will work to reduce the likelihood of delayed CINV, without seeing any efficacy data, would you have any reasonable expectation that it would, in fact, work for that purpose?

A. I think it would be fair to say the answer to that would be no.

Q. Dr. Markman, if you could turn to Page 616 of Exhibit 4 in your 2002 paper.

Is it correct in Table 4 you set forth here the best options at the time to try to treat delayed CINV?

A. I believe those are -- I list two regimens. Those are perfectly reasonable regimens at that time, yes.

Q. One of them was ondansetron plus dexamethasone, 8 milligrams orally each twice a day?

A. Yes.

Q. Maybe if we can take a look at Page 615 of your article. And you see here listed as serotonin receptor antagonists dolasetron, granisetron, and ondansetron?
A. That's correct.
Q. Does that refresh your memory that those three setron molecules that are listed in Table 2 were available for treatment of CINV in 2002?
A. I think that's probably what I mean there.
Q. Right. And, so, what -- what I'm getting at is these three molecules, for example, dolasetron, granisetron and ondansetron, had significances in pharmacokinetic and pharmacodynamic process, correct?
A. Again, that's not my area of expertise.
MR. O'MALLEY: Maybe it's me, but I think there was a key mistake there. He didn't say "palonosetron," but --
THE COURT: Let's back it up.
THE WITNESS: Again, that's not my area of expertise, but I certainly would accept the argument they were not the same drugs.
Q. And despite the -- does that refresh your memory that those three setron molecules that are listed in Table 2 were available for treatment of CINV in 2002?
A. I think that's probably what I mean there.
Q. Right. And, so, what I -- what I'm getting at is these three molecules, for example, dolasetron, granisetron, and

ondansetron had differences --

THE COURT: Right. In the dep transcript the word "palonosetron" is incorrect, and it should be replaced with "dolasetron," right? Dolasetron.

MR. ASHKENAZI: Yes, your Honor.

THE COURT: Okay. We can go on.

Q. This is in pharmacokinetic and pharmacodynamic processes, correct?

A. Again, that's not my area of expertise, but I certainly would accept the argument they were not the same drugs.

Q. And despite the differences they had with respect to those properties, clinically they were considered equivalent in terms of efficacy and toxicity in 2002, correct?

A. Yes. I believe they were essentially equivalent in terms of efficacy, and I -- I believe pretty much in terms of toxicity.

Q. Can you turn to Page 616. I want to focus you on the bottom right paragraph on that page, starting "Recent data suggest." Do you see that?

A. Yes.

Q. I'll read it for the record. It states, "Recent data suggests that a new class of agents, neurokinin-1 receptor antagonists, may be particularly effective in preventing delayed emesis due to highly emetogenic chemotherapy such as high-dose cisplatin."

Do you see that?
A. Yes.
Q. And do you agree that that sentence reflected the state of the art in antiemetics in 2002?
A. Well, I think the statement is correct.
Q. It was correct in 2002 was, I guess, my question?
A. Yes. Yes.
Q. As the paragraph continues, is it correct that these NK-1 receptor antagonists were also believed in 2002 to potentially be able to increase the effects of 5-HT_3s preventing acute CINV?
A. There was certainly data to support that, yes.
Q. Do you recall that Dr. Amidon talked about certain 5-HT_3 compounds that were touted as promising in the 1990s, but had been abandoned by 2002?
A. I do not remember the specific statement, but I certainly would accept that statement as being correct.
Q. But to go back to the original question, do you agree that it was known in 2002 that there were at least certain setrons that were touted as promising only to have been abandoned in advance of the January 2002 date?
A. Yes.
Q. Can we please turn to your opening report, Exhibit 33. I'm sorry, Paragraph 33.
A. Okay.

Q. In this paragraph you discuss the Eglen 1995 article; is that correct?
A. That's correct.
Q. And as a preliminary matter, I just want to confirm that you rely on Eglen 1995 only as support for your opinion that palonosetron would have been a molecule that a POSA would have been motivated to pursue, correct?
A. That's correct.
Q. You're not using any preclinical data in Eglen to try and compute what human dosage might be --
A. No.
Q. -- that would be efficacious?
A. No.
Q. In your experience, have you ever heard of scientists relying on animal data to estimate a human dose when there was human clinical data available with respect to that molecule?
A. Well, I guess all I would say is it usually goes the other way around.
Q. Right. So in your opinion, you would not look to preclinical data to attempt to extrapolate a human dose?
A. That's correct.
Q. If you turn back to the right side of 865, the second-to-last sentence of Eglen states, "As the present study lacks extensive antiemetic efficacy data with granisetron, it is unclear as to how palonosetron would compare with

granisetron."

Do you see that?

A. Yes.

Q. The Eglen 1995 authors are stating here that potency comparisons between palonosetron and granisetron cannot be made based on the preclinical data they present, correct?

A. Well, that's true because they studied ondansetron and -- well, they did. Hum.

Well, in this particular animal model, they did have granisetron in it at Table 1, so I'm not exactly sure why they made that statement, but they did make the statement.

Q. Would you agree that a POSA reading Eglen 1995 wouldn't draw any conclusions about the relative potencies of palonosetron and granisetron based on the data in Eglen 1995?

A. I would certainly think that's a reasonable conclusion.

Q. I'm now showing you what's been marked for identification as Exhibit 11. This is an abstract from an MACC meeting from June 23rd to 26th 2002 in Boston, correct?

A. Yes.

Q. If you can take a look at the abstract, can you confirm, and please take the time to read the abstract, for me that what's being reported here is that a 0.25-milligram dose of palonosetron was found to be effective in treating CINV?

A. Yes. The answer is yes.

Q. The information in Exhibit 11 would have been well known

to a POSA as of January 30th, 2003, correct?
A. You mean six months later after this, yes.
Q. I'd like to turn next to your opinions on secondary considerations, and maybe we can take a look at your reply report to get the context.

Well, first let me ask you a general question: For a given pharmaceutical drug product if that product is not sufficiently stable to be shipped and stored, is it correct that that formulation could not be used to treat patients?
A. Well, obviously you're -- you're talking to a clinician about pharmaceutical product issues at a basic level, so, you know, I could be wrong on this, but it certainly would seem to me that you would need to have it stable to be shipped and stored.

Now, that being said, there are -- obviously things get shipped in certain ways and then they get, you know, combined and -- at the time of administration. So, the way you ship it is not necessarily the way you give it, but whatever you ship and in some way it's got to be stable to allow you to do whatever you need to do later.
Q. So, do you agree that unless a pharmaceutical product has sufficient stability, that it would not be efficacious enough to treat patients?
A. I mean as a general statement, sure, that's absolutely true.

Q. Dr. Markman, could you please look at Footnote 17 on Page 17 of your rebuttal report. And can you please read that paragraph to yourself and let me know when you've done that.

A. Yes, I have.

Q. What did you do to formulate the opinion in this footnote that Aloxi®'s antiemetic activity is due solely to palonosetron, not the formulations claimed in the '219 patent?

A. I don't remember specifically what I looked at, but there's obviously information that it has -- it's been given in other ways and shown to be effective.

MR. ASHKENAZI: Your Honor, that's the end of this video deposition.

THE COURT: Okay. Fine. Thank you.

MR. ASHKENAZI: Would you like to move on to the next one?

THE COURT: How long is the next one?

MR. ASHKENAZI: About an hour and 17 minutes, your Honor.

THE COURT: Okay. Sure. Well, let's get started.

MR. ASHKENAZI: So your Honor we'll be playing now the deposition testimony of Dr. Valentino Stella. We submitted a declaration which corresponds to DTX-1037 in connection with the prosecution history of the '725 patent.

Dr. Stella was deposed by defendants in this case. Dr. Stella is a distinguished professor in pharmaceutical

chemistry at the University of Kansas where he has taught since 1973. Dr. Stella focuses his research on formulation design and delivery and has more than 40 years of experience in the pharmaceutical industry.

THE COURT: Let me just review that for a second. Give me a moment.

MR. ASHKENAZI: Sure.

THE COURT: You said he was deposed by defendants?

MR. ASHKENAZI: Yes. So he submitted a declaration during the prosecution of one of the patents in this case, the '725 patent, and as the declarant, the defendants deposed him during, I believe, fact discovery.

THE COURT: Isn't he defendants' expert?

MR. ASHKENAZI: This is Dr. Valentino Stella. So the defendants' experts we've been talking about were Dr. Markman, which we just heard, and Dr. DeLuca which we'll hear at a later point in time. This is some additional deposition designation testimony that the plaintiffs would like to introduce into the record.

THE COURT: I'm trying to understand. Is he your expert?

MR. ASHKENAZI: He's not an expert. He was a declarant during the prosecution of the patent.

THE COURT: Oh, now I remember. It's been so long. I'd forgotten that he did a declaration, and he did it on

behalf of Helsinn --

MR. ASHKENAZI: That's correct, your Honor.

THE COURT: -- in the patent prosecution.

MR. ASHKENAZI: That's correct, your Honor.

THE COURT: All right. Let me just make a note of that.

And that was prosecution of the '725 patent?

MR. ASHKENAZI: Yes, your Honor.

THE COURT: So, question to defense counsel: I take it you don't have any objection to the use of these deposition excerpts, do you?

MR. LOMBARDI: No, your Honor.

THE COURT: Okay. Fine. So, this is like -- we used to call it a de bene esse deposition. Today they're called trial depositions. Is that basically what it is?

MR. LOMBARDI: It's a fact witness whose testimony was preserved and is being presented.

THE COURT: Fine. Off we go.

MR. ASHKENAZI: So, your Honor, for the record, there are four documents that are going to be referenced during the deposition, and we'll be pulling them up, as well, but Stella Exhibit 160 referenced during the deposition corresponds to DTX-1037. Stella Exhibit 163 corresponds with PTX-295. Stella Exhibit 164 corresponds to DTX-983, and Stella Exhibit 165 is DTX-345.

(The video deposition of Valentino Stella played in open court:)

Q. Will you please state your name for the record.

A. Yes. It is Valentino Stella.

Q. Are you currently employed, Dr. Stella?

A. Yes. I'm employed by the University of Kansas.

THE COURT: Too loud. Way too loud.

Q. And what is your position there?

A. I'm a university distinguished professor of pharmaceutical chemistry.

Q. So, Dr. Stella, I just wanted to go through a little bit of your educational background, if we could. So, could you give me your education background starting with your college degrees?

A. Okay. I -- I graduated -- I have a bachelor of pharmacy degree from the Victorian College of Pharmacy. Victorian College of Pharmacy, now part of Monash University, M-O-N-A-S-H. I got a bachelor of pharmacy. I actually completed my education in '67, but the degree wasn't given until '68.

Q. Okay.

A. I then worked as a hospital pharmacist for one year in Australia. And in the fall of 1968, I was accepted into the Ph.D. program at the University of Kansas to study under the late Professor Takeru Higuchi, T-A-K-E-R-U. Last name is

Higuchi, H-I-G-U-C-H-I.

And I started in the fall of '68, and I completed my doctorate in the late summer of 1971. And after that I started -- I got my doctorate with honors, and then I, again, was employed. From that point on was in -- at various -- at two universities. Do you want information on that?

Q. Yes. Could you tell me what the two universities that you were at?

A. Right. I was on the faculty of the University of Illinois in Chicago, Medical Center, in the school of pharmacy. And taught various classes and performed research.

And then in the summer of 1973, I'd been recruited to return to the University of Kansas. So, in 1973 I returned to the University of Kansas as an assistant professor and subsequently proceeded through the ranks at KU.

Q. So, following your -- the receipt of your Ph.D. in 1971, your entire career until this point has been in academia; is that correct?

A. My ac -- my academic career has been that, but I've started three drug companies.

Q. Okay.

A. I started three drug companies, inventor/co-inventor of about eight products on the market, and I've consulted for the pharmaceutical industry since 1972. So since 1972, the last 41 years, I've extensively worked with the pharmaceutical

industry. In fact, I did an evaluation not too long ago of how many companies I've consulted for, and it was over 100 in that 42 years.

And, so, I've been involved in a lot of drug product development, my own as well as other companies -- with companies. So, I have a lot of industrial experience, but I've never worked for the pharmaceutical industry, per se.

Q. You stated that you had started three drug companies. Could you tell me a little bit more about the three companies?

A. I started -- the first company I started was a company called Cydex, C-Y-D-E-X. It's now actually part of Ligand, L-I-G-A-N-D. It was a company that started to develop, market, sell a cyclodextrin, C-Y-C-L-O-D-E-X-T-R-I-N called Captisol, C-A-P-T-I-S-O-L, which is a novel formulation development excipient for dissolving drugs, and that company is now -- as I said, is now part of Ligand.

I also started a called ProQuest, P-R-O-Q-U-E-S-T, Pharma. ProQuest Pharma is -- was a prodrug company, P-R-O-D-R-U-G, company. And we successfully launched one drug product called Lusedra, which is actually now marketed by Eisai. I better get my companies right. Yes. Eisai.

And that company -- we sold that company to Gilford Pharma that was bought by NGI Pharma that was bought by Eisai, so it's --

Q. Okay.

A. Okay. And the last company is still a functioning company called CritiTech, C-R-I-T-I-T-E-C-H. CritiTech. That's in Lawrence, Kansas. That uses a super critical carbon dioxide for various pharmaceutical processing.
Q. So, at ProQuest Pharma, you said you launched a drug called Lusedra. What was the -- what was Lusedra indicated for?
A. It's an anesthetic drug.
Q. And in what form is it administered to a patient?
A. It's injectable.
Q. Injectable. You also stated that you were an inventor or co-inventor of eight, was it products or patents?
A. No. I have 39 patents.
Q. Okay. So, you're a co-inventor or an inventor of?
A. Well, it depends on how you count. So, there's -- I have a drug fospropofol -- fosphenytoin. I have a drug called fos -- Lusedra, which is fospropofol. I'm the co-inventor of Viread, which is a top-selling aids drug with Gilead. I'm the co-inventor of the formulation of Velcade, which is an anti-cancer drug, and then Encapusol, which is the solubilizing agent. It is in eight commercial -- six FDA-approved commercial products. So, it depends on whether you count the drugs' products.
Q. Viread, is that -- how is that -- and what is the dosage form for Viread?

A. Viread is an oral dosage form.
Q. And Velcade, what is the dosage?
A. That's injectable.
Q. So, you're -- you said you have extensive experience in drug product development?
A. Yes.
Q. Is most of that experience as a consultant for pharma companies?
A. No.
Q. It's then work that you've done for your products?
A. Also for the 30-odd years I had a contract with the National Cancer Institute for developing formulations of problematic drugs for lonely injectables --
THE COURT: Stop it. Anyone want to guess what the proper word there is instead of "lonely" drugs?
MR. LOMBARDI: Maybe "not only."
MR. O'MALLEY: I thought it was "mainly," but I'm guessing.
THE COURT: Problematic drugs for -- let's listen to it again. It is probably not significant, but it just looks funny on the record. Go ahead. Back it up. Please.
THE WITNESS: Also, for 30-odd years I had a contract with the National Cancer Institute for developing formulations of problematic drugs for the only injectables.
THE COURT: Let's just go on.

THE WITNESS: Problematic drugs, injectable drugs. Besides parenteral. Did I say that word? Yeah. Parenteral is P-A-R-E-N-T-E-R-A-L, which is another way of saying injectable drugs. And I had that contract for -- since 1983, and it just expired last year. So, I did that for 30 years. If I got the numbers right. Yeah.

Q. I probably can't figure out the math right now either.

If you have to estimate, you know, percentage of your work that you've done on parenterals, could you give that number?

A. I'd say about 50 percent, yeah.

Q. Okay.

A. But it may be a bit higher, maybe lower.

Q. All right. I'm going to ask the court reporter to mark another document as DX160. Dr. Stella if you could take a moment and just review the document. Do you see that this is this document the title is, "Statutory Declaration of Valentino J. Stella"?

A. Yes.

Q. Is Valentino J. Stella, is that you?

A. Yes.

Q. And can you turn to the last page of the document. And there's a signature there on that towards the top of the page. Is that your signature, Dr. Stella?

A. Yes, it is.

Q. If you turn to the second page of the document, do you see at the top of the page there's a reference to an application number?
A. Yes.
Q. It's PCT, and I'll read it into the record PCT/EP2004/001558?
A. Yes.
Q. This declaration, Dr. Stella, was submitted in connection with that application; is that correct?
A. The best of my memory, that's correct.
Q. Did you prepare this declaration, Dr. Stella?
A. Yes.

THE COURT: Could we stop there for a second? Counsel, maybe you can help me. The first page had the application number as what we referred to as the 268 application, and I have been told that the 268 application corresponds to the '725 patent, but now in this most recent portion of the video he is being directed to some sort of document that ends in 558, so I don't follow.

MR. ASHKENAZI: Your Honor, the -- I believe that's the second page of the exhibit, so the cover page referenced the serial number at the top right if we can go to DTX-1037-0001. And the second page of that document, your Honor, of what he signed had a different reference to an application number, and I believe it is just a corresponding

PCT number.

THE COURT: What is "PCT"?

MR. ASHKENAZI: Patent Cooperation Treaty.

THE COURT: European?

MR. ASHKENAZI: Foreign -- I guess it is a foreign filing. That's what the EP reference is, but I can confirm for your Honor during one of the breaks.

THE COURT: Well, I'm only asking whatever that 1558 number is, is it still -- is this document a declaration that was submitted to the USPTO under application number 11/388,268 and I think it was.

MR. ASHKENAZI: That's correct, your Honor.

THE COURT: So I needn't be distracted with this 558 number?

MR. ASHKENAZI: Absolutely not.

THE COURT: Do you agree, Mr. Wong?

MR. WONG: Yes.

THE COURT: Fine. On we go.

Q. And do you recall when you prepared the declaration?

A. Around the date that it was signed. I don't know specific dates.

Q. Okay. Why did you prepare this declaration in connection with this application?

A. To the best of my recollection I was asked to provide support for the stability of the drug, some of the concerns

associated with that, and I wrote this -- this declaration in response to that.

Q. And who asked you to prepare the declaration?

A. I believe it was the lawyer involved in this particular case. Oh, I'm drawing a blank on his name.

Q. Okay. That's fine. Do you know if it was a lawyer for Helsinn?

A. I don't remember.

Q. And, so -- do you know if it was a lawyer for Roche?

A. I don't know how to answer that question.

Q. Okay.

A. I just remember the name of the lawyer now. It is Clark Sullivan.

Q. Okay.

A. Okay. Go ahead.

Q. That's fine.

THE COURT: He said "go ahead."

A. It was Clark Sullivan. I assume I think he was representing Helsinn.

Q. So, if we looked at Paragraph 5...

THE COURT: Okay. This is a perfect time for a recess.

(Brief Recess.)

THE COURT: Continue.

(The video testimony of Valentino J. Stella was played.)

THE COURT: Could we just back it up so we know where we are?

Q. So, if we looked at Paragraph 5 of your declaration, you write there, "Two of the primary issues affecting drug delivery are the solubility and stability of the molecule."

Do you see that?

A. Um-hum.

Q. Why was it your view that two of the primary issues affecting drug delivery were solubility and stability?

A. I guess I'm really referring to the formulation of drugs.

Q. Okay.

A. You know, it's -- you know, it's probably not clarified enough, but it's really -- I'm really talking about here issues associated with the formulation of drugs. Those are two major concerns. There are other concerns, but those are two major concerns.

Q. Is preformulation always a part of formulation of the drugs?

A. Traditionally that would be the case and it would be particularly the case in this time frame.

Q. And what -- what are the types of studies that are done in the pre-formulation stage?

I'm asking -- I'm asking in general just based on our discussion here on formulation development.

A. There are things that people -- that are done, okay, such

as solubility, stability, other properties of drugs' molecules.

Q. But preformulation is typically done in the development of a -- and as part of formulation development for a drug?

A. In that time frame there were usually groups that did preformulation studies.

Q. Okay. And aren't stability and solubility determined at that point or at the preformulation phase?

A. The beginning of that process is usually done at that stage.

Q. I just wanted to ask you, though, from a -- and to the extent that you know, from a regulatory perspective, is there a requirement that a drug have a stability at room temperature for two years in order for it to be approved?

A. I don't know if there's any specific regulatory requirement for that. I just know that that's the goal that you aim for. If there's something less, I know there are some products that have been approved for, you know, storage at temperatures other than 20 -- at room temperature.

Q. Uh-huh.

A. And there are products that have shorter shelf lives than two years. But I've not been involved in that from a regulatory point of view, at least in my personal experiences. So I think it's getting outside of my specific area of expertise.

Q. Okay. But in your -- as you stated, in your -- in your -- you are familiar with drugs that have been approved with less than two years' stability and that are not necessarily stored at room temperature; is that correct?

A. Either/or, yeah. Yeah. I am familiar with that, yeah.

Q. Okay. Can we look at Paragraph 6 of your declaration.

And I'll just read it, that sentence, into the record: "I have authored or co-authored numerous peer-reviewed articles on subjects relating to drug stability and solubility, in addition to the following textbooks on the subject, among others."

And then you list three textbooks there. Do you see that?

A. Um-hum. Yes, I should say. I should say -- not say "um-hum." Yes.

Q. My question to you, Dr. Stella, is: Do you recall why you listed these three particular textbooks in the declaration?

A. Okay. I don't remember the specifics, but these are three books, major books, that I've authored and co-authored, all of which have issues associated with stability and solubility of drugs. And just -- really just speaking to my qualifications, more than anything else.

Q. And these books, who are they directed to in terms of the audiences? Is it pharmacists, academics, people in industry?

A. All of the above.
Q. Do you remember -- or, sitting here today, do you recall whether you prepared this declaration in connection with the Calderari application as referenced on the front of Exhibit DX-160 or the PCT application that's referenced on the second page of your declaration?
A. I don't remember. I mean, I assume it is the Calderari, and there may be other data. I don't have any recollection for that.
Q. Okay. Can we just look at Paragraph 9. And I just have -- if you can take a moment and review that, I have a question for you.
A. Okay.
Q. You list there a number of chemical degradation pathways and mechanisms that a drug can undergo; is that correct?
A. Um-hum. That's correct.
Q. Now, my question for you is: With respect to a drug that's being formulated as a parenteral, are any of these pathways or mechanisms that you've listed here more significant than others?
A. It depends on the drug molecule.
Q. Can you make a general statement about whether any of these pathways that are listed here for drug products would be more common than others?
A. Well, all of these are possible. I mean, it really

depends on the structure of the drug molecule. And it also depends on the time frame that you -- that you're talking about.

Q. I'm going to ask the court reporter to mark as Exhibit 163, a document.

So, the first question I have for you: This is a -- this document on the front of it, the first page states, "Chemical Stability of Pharmaceuticals, A Handbook for Pharmacists."

Do you see that?

A. Yes.

Q. And you're listed there as an author of that book; is that correct?

A. Yeah, I'm a co-author of the book.

Q. And this document is excerpts from that book that you co-authored?

A. Yep.

Q. Okay. And if we look at your declaration again, this book is listed as one of the three books that are specifically mentioned in Paragraph 6. Do you see that?

A. Yes.

Q. Can you confirm that for me, please?

A. Right. That is correct.

Q. Okay. If we turn to five pages in, and beginning of Chapter 4 of your book -- and I think you just passed it. Go

back one.
A. Oh, Page 4. Okay.
Q. Yes.
This chapter talks about hydrolysis and other ACL transfers. Do you see that?
A. Yes.
Q. Okay. And there's a -- in the first paragraph that's on that page -- and I'm just going to read it into the record. It's the second sentence of -- or I'm sorry. The third sentence of first paragraph and I'll just read it into the record. Quote, it states, "Despite the large number of possible reactions leading to drug degradation, many, perhaps most of those that do occur can be classed as either hydrolysis -- hydrolyses or oxidations."
Do you see that, Dr. Stella?
A. Yes.
Q. Do you agree with that statement?
A. Yeah, it's -- yeah.
Q. Okay. So, in Paragraph 9, if we look at Paragraph 9, you list a number of pathways and mechanisms.
Is it correct to say that oxidation and hydrolysis are common pathways for drug degradation, the ones that you listed there?
A. Those are, you know, major pathways for degradation of some drugs, yes.

Q. And, in fact, in your book that you -- you state that most -- for -- for drug degradation, of the possible reactions, most of those that do occur are either hydrolysis or oxidation; isn't that correct?

A. They are two of the major pathways, yes.

Q. Okay. Thank you.

And then if we move on to Paragraph 10, you talk about palonosetron in there. You state -- and I will read the sentence into the record: "Palonosetron is notable in this respect because it lacks any of the structural features that commonly favor structural degradation."

And then you go on to list the features that favor structural degradation; is that correct?

A. That's correct. The only issue I had in reviewing this was with the amides, and -- amides, A-M-I-D-E-S. And I guess what I'm saying here is that the -- that hydrolysis occurs, depending on the structure of the drug. Palonosetron does have an amide structure in its functional group, in its structure, but its functional group is such that it's a functional group -- an amide group that is structurally -- is generally considered to be quite stable.

So what I'm really referring to here is compounds that are sensitive to the degradation, is structurally sensitive.

So, for example, esters, an ester group, is -- can be unstable, but they're also very stable, ester groups.

So -- and what I'm really saying here is really related more to those compounds with those groups are in an activated state, and that's not the case with palonosetron. So this is actually a poorly worded statement in some ways.

Q. Okay. So let me just break that up a little bit.

A. Yeah.

Q. Just the -- the first question, I guess, is palonosetron does have an amide?

A. It does, yeah.

Q. So your statement in -- in that paragraph that it -- to the extent -- strike that.

To the extent that your statement in that paragraph suggests that palonosetron does not have an amide, that was incorrect; is that correct?

A. What I -- what I did -- no, it's not a misstatement. What I -- what I -- sorry. It was a mis -- you're mischaracterizing it. What I'm -- what I was saying here is that there are structural groups that are subject to hydrolysis, but not all ester groups, not all amides, not all other groups are necessarily unstable for that specific drug. Okay? So...

Q. This paragraph, though, Dr. Stella, is talking specifically about palonosetron --

A. Yes.

Q. -- is that correct?

A. And -- and, but I'm saying it doesn't have an amide group that would be subject to hydrolysis, a significant rapid hydrolysis.

So I think it's just the way the word is -- the way it's framed a little bit.

Q. But it doesn't say that specifically, that it doesn't have an amide group that would be subject hydrolysis --

A. No, it does say lacks any of the structural features that commonly favor structural degradation. By that I meant rapid degradation that we have to worry about.

Q. But you didn't say that in Paragraph 10, that commonly favor rapid degradation.

A. Commonly --

Q. Is that correct?

Dr. Stella, I guess I'm trying to understand, you're trying to explain that your statement there that palonosetron lacks structural features that commonly favor structural degradation was poorly worded because palonosetron doesn't have an amide. I'm trying to understand what part of Paragraph 10 was incorrect then.

A. There's nothing incorrect.

Q. So...

A. It -- when I said "commonly favor structural degradation," meant that it would have an amide group, for example, that was an activated amide group that would degrade

rapidly.
Q. But you didn't state that in here in Paragraph 10.
A. I didn't state it clearly enough.
Q. Okay. Can we look again at your book, please.
Before we do that, I just have a question.
Are amides subject to degradation only through hydrolysis?
A. Hum, good question. We could get esoteric here and I could say, yes, there's other mechanisms, but that's the major -- major pathway. If it's an activated amide, that -- hydrolysis is the principal reaction. There's rearrangements that can occur, but there's nothing in this structure that would suggest that.
Q. Can an amide be subject to oxidation?
A. That was one of the things I thought about when you asked the question. It can if the -- if there's no N-substitution. But it's fairly rare.
Q. So the amide would be susceptible to oxidation if there was an N-substitution? Is that what you're saying?
A. No. I'm saying if there's not a substitution, an N-substitution, you can sometimes form an N-oxide of that. But that's very rare. I can't -- I can't -- I can actually not think of a cyclic example that comes to mind, so it would be pure speculation.
Q. So your opinion is that it's very rare that an amide is

susceptible to oxidation?

THE COURT: Okay. Could we stop there?

(Video stopped.)

THE COURT: The transcript said, "You can sometimes form an oxide of that," and what he said was, "You can sometimes form an "anoxide" of that," and understood that way it makes sense.

MR. LOMBARDI: N, as in the letter N.

THE COURT: Is it N?

MR. LOMBARDI: That's our understanding.

THE COURT: Not A-N?

MR. LOMBARDI: Right. Well, there are places -- I'm not sure of the exact spot Your Honor was looking, but there are places where I think that it was transcribed as "end oxide," and I think he was saying "N," the letter "N."

THE COURT: With a hyphen?

MR. LOMBARDI: Yes, that's how it would usually be portrayed on the page.

THE COURT: Okay. Could we go back and just let our court reporter properly get down what he says in that sentence where the dep transcript says "form an oxide." And we can instruct the reporter that if she hears "an oxide" as one word, it's the "N-oxide" term. Is that agreeable, counsel?

MR. ASHKENAZI: Yes, Your Honor.

THE COURT: Okay. Let's go back and listen. Not

that I understand, but we'll listen.

(Video continued.)

Q. So the amide would be susceptible to oxidation if there was an N-substitution, is that what you're saying?

(Video stopped.)

MR. LOMBARDI: N.

THE COURT: Instead of E-N-D, he's saying "N-substitution"?

MR. LOMBARDI: That's right.

THE COURT: Referring to nitrogen, N?

MR. LOMBARDI: I actually don't think it's referring to nitrogen.

MR. O'MALLEY: It is.

MR. LOMBARDI: Is it?

MR. O'MALLEY: The nitrogen.

MR. LOMBARDI: Okay.

MR. O'MALLEY: I think what he's saying is that the nitrogen has a substituent group on it. It could be susceptible to oxidation is how I understand.

MR. LOMBARDI: And we think that's right.

THE COURT: It makes it difficult to get it right on paper. So let's go back.

(Video continued.)

Q. So the amide would be susceptible to oxidation if there was an N-substitution? Is that what you're saying?

A. No. I'm saying if there is not a substitution, an N-substitution, you can sometimes form an N-oxide of that, but that's very rare. I can't -- I can't -- I can actually not think of a cyclic example that comes to mind. So it would be pure speculation.

Q. So your opinion is that it's very rare that an amide is susceptible to oxidation?

A. Sitting here today, I'm drawing a blank on -- on how it might, but --

Q. Okay.

A. -- but I'm willing to be corrected by the literature.

Q. All right. Is an amine different from an amide?

A. Yes.

Q. Okay. And are amines subject to oxidation, do you know?

THE COURT: Stop, please.

THE WITNESS: Amines can --

(Video stopped.)

THE COURT: Counsel, if you'll look at Paragraph 10 of his declaration that we have highlighted, blown up here, he spells it I-M-I-N-E there, the first word on Line 5.

MR. ASHKENAZI: Your Honor, there are three different types of compounds, amides, imines, and amines -- amides, imines and amines, so they are actually different substituent -- different substituent groups. He's referring to an amine, I believe, in this context.

THE COURT: Paragraph 10 of his declaration does not contain the word "amine," A-M-I-N-E, does it?

MR. ASHKENAZI: Sorry, the question, I believe.

MR. LOMBARDI: Yeah, I think what's happening is that the declaration does use, I'll just say "imine" to try to be clear, and I think he's now in the questioning talking about "amine" which is different.

MR. ASHKENAZI: That's my understanding as well.

THE COURT: Okay. So let's hear it in the deposition, the question about amines again.

(Video continued.)

Q. And are amines subject to oxidation, do you know?

A. Amines can -- the nitrogen on the amine itself can undergo oxidation, and the carbons neighboring the amine can undergo oxidation. So it's a very complex question, actually, to ask. It's more complex than you probably realize it is.

Q. Okay. If we can look at the structure of palonosetron that you set forth there in your declaration.

Can you tell me, Dr. Stella, are you familiar with a cyclic amide referred to as a lactam?

A. As a lactam?

Q. Yeah, lactam, L-A-C-T-A-M.

A. Lactam?

Q. Yeah, lactam, yes.

A. Lactam, okay. Yes.

Q. Does palonosetron have a lactam?
A. Yes. It's a six-member lactam.
Q. Okay. If we can move forward in your declaration to Paragraph 12. You state there, and I'll read it into the record: "If degradation of palonosetron were suspected, one could not predict from the structure of the molecule how the degradation was occurring. Additional information and teachings would be required."
My question to you, Dr. Stella, is: What did you mean by "additional information and teachings would be required"?
A. I'm basically saying in this paragraph that when I was given the structure of this compound, would I have a priori predicted that this compound would be chemically unstable. And the answer was no. Okay? The additional information would be -- provide me with data to show what the degradation products are. Okay?
Q. Okay.
A. And then -- then I could tell you whether that made sense, whether it was unusual, whether it was novel and whatever. I would have to know more about either the -- probably the degradation products as well as the conditions under which experiments were performed to be able to say that the degradation was significant, and, therefore -- and what was the possible and probable mechanism.
Q. Dr. Stella, do you know if you asked for any of that

additional data that you just mentioned?
A. I don't remember.
Q. And you don't remember whether you reviewed any of that type of additional data that you just mentioned?
A. As I told you, I don't remember.
Q. So, at the time that you wrote this declaration, you don't remember whether you had seen any data from the applicant regarding the possible degradation products of palonosetron?
A. I don't know.
Q. If you had seen that type of data, would you have included that as the data you reviewed in Paragraph 8 of your declaration?
A. I don't -- I don't remember the circumstances. So I can't -- you know, I don't know that I can answer that question.
Q. Um --
A. Put it this way. I would not have -- -- I would have answered to the best of my ability, provided -- you know, with the data that was provided, right? So I -- yeah. I don't know any more than that. Don't remember any more than that.
Q. Dr. Stella, before the break, we were on Paragraph 12 of your declaration, which is Exhibit 160. And I had asked you a question. I'm just going to ask it again.
There you state -- in Paragraph 12 you state that

additional teachings would be required, and my question to you is: What would those additional teachings be?

A. I think I answered that question earlier. That is what the structural -- what the structure of the degradation products were.

Q. Do the degradation products of a drug depend on whether it's in solution or not?

A. It can.

Q. Let me -- sir, then let me ask you this question: Can you always predict from the structural formula -- formula whether degradation will occur for a drug that's in solution?

A. I wish I could. Let's just say that, you know, as one of the top experts in this field, I've got a pretty good chance of predicting that compared to someone normally skilled in the art. But I would not -- you know, science would not be necessary if we could do that. I mean, we could just predict it and go on and not have to do any experiments.

So in this case -- in many cases we get thrown curve balls. And the curve balls are what makes science interesting, right? Because it's -- well, why is that unstable? So we think we're pretty smart, but we're not.

You know, at the end of the day, it depends on the individual drug, individual structure, what's there, and that's the -- the coalescence of all those factors are going to determine whether the drug is going to be unstable or

stable, based on the structure. We can have a guess sometimes and we're right. If you're smart and you know the literature, you can be right a lot of the time, but you're never going to be perfect.

Q. And so you would need to do experiments to determine whether there -- a particular drug was susceptible to degradation?

A. Properly designed experiments can help you build your foundation for what's going on with that specific drug.

Q. And I will -- I will ask that question again, just to make sure it's clear.

In formulation development, is it common practice to determine the potential degradants for a drug substance under investigation?

A. Stability of degradation products are done.

THE COURT REPORTER: I'm sorry?

THE WITNESS: What did I say? The isolation and identification of drug degradation products is done. However, we have to be very careful when you do that because degradation products that might occur in the early stage of drug development may not be the same degradation products we see in the formulation because that is sometimes determined by the conditions of the formulation.

So I've had lots of examples where we have drug degradation products, we think of the major degradation

products, and yet when we go to the formulation, we see another degradation or different degradation product. So it's just part of a -- of a very complicated process and unpredictable nature of drug stability, that requires us to be very careful and very diligent when we perform those studies.

Q. And for a drug that's in solution, pH certainly can have an effect on stability; isn't that correct?

A. Stability -- pH can influence the stability of drugs, yes.

Q. And the particular excipients that might be included in a formulation of a drug that's in solution can certainly affect the stability of that drug; is that correct?

A. The components can have a positive or a negative influence.

Q. Now, does the drug concentration have an effect on the stability of a drug that's in solution?

A. It can influence it, again, positively or negatively.

Q. Are there any general rules of thumb concerning how drug concentration might impact stability?

A. I could give you examples in my own work where it's gone both ways. So I can't -- I don't know that I would give you a general rule of thumb for all degradation pathways.

Q. So that ultimately is something that needs to be determined as part of formulation development for a drug; isn't that correct?

A. It is -- yes, it requires significant experimentation to make -- to confirm whether there is a concentration dependency or not, positively or negatively.

Q. What do you mean by "significant experimentation"?

A. Well, let me give you something that is always dangerous for us to do. If we -- when we do initial, what I call preformulation workup of drugs, very often we're operating under relatively dilute solutions. Okay? We're looking at what the major degradation pathways are, under conditions that I would say are not necessarily formulation conditions.

So we often get pathways of degradation or kinetics of degradation that -- now, in a lot of the anticancer drugs that I've had to develop, the formulator or the company or the International Cancer Institute says, we want to achieve this concentration. Often when we -- we have trouble reaching that concentration just because it's a solubility limit. All right?

So, when we have to come up with novel ways of getting the solubility up, the stability can dramatically change. And so you have preformulation studies that might give you one answer, and you may have formulation studies that give you a completely different answer, and we have to figure out what the heck's going on, and if we change another variable, what's that going to do.

So the whole issue of drug stability from

preformulation to formulation is a very complex process, not something that's -- that -- it's something that has to be done very carefully with good experimental design. Okay?

Some people get to the end product empirically. They don't necessarily do good design, and they could be lucky, or they can go to that same spot, do it empirically, and they've got a massive failure on their hands, you know, in different phases of clinical development.

So this whole process is a very complicated process. We've gotten better at it with time, but based on work that I've seen around the industry, et cetera, as a consultant to the pharmaceutical -- and from my own experience in the lab, I usually use a more colloquial term, but let's say Mother Nature throws you a curve ball a lot.

Q. When you say that it's a complicated process, you're talking about -- are you talking about in terms of the -- the time commitment versus the actual experiments that need to be done?

A. Often both.

Q. Okay. Would you agree that in formulation development, there are typically stages that you go through in terms of developing a formulation?

A. There are experiments that are done, but a good researcher in a formulation group in a drug company, I would hope, would be smart enough to not always follow a routine,

but to use their smarts to come to the end result based on initial observations. So, the word "a routine" or "typically done," I think is a bad word to use here. There is no typical or routine because every drug molecule is different.

Now, often if you're working within a narrow class of compounds that you've got a lot of knowledge on, you can go off into the end result fairly quickly.

But when you have complex drug molecules, one of the things I tell my students -- I just finished teaching a three-credit drug stability class. I said, you know, one of the advantages of being in the pharmaceutical sciences, every molecule is new and have -- and contain multiple functional groups.

So while a physical organic chemist at the University of -- at Harvard University is often counting the number of angels on a pinhead for a very simple, straightforward reaction, we have to deal with very, very complex molecules where there's a lot of interaction between functional groups.

And so it makes our life a lot more exciting because you'll get a molecule, you think you know what will happen and, bingo, it's not doing the -- you can't follow the, quote, unquote, something that has some -- is done on a relatively bang, bang, bang basis. We generally have to really modify how we think about every molecule almost that we come across, especially the molecules that I've had to work with.

Q. So you don't like to use -- you don't like the use of the word "routine" to describe formulations at all; isn't that correct?
A. To be fair, there are some steps that people begin, but they usually divert very quickly once you get into the process, just because of the complexity of drug molecules.
Q. We can look at Paragraph 13 of your declaration. And if you can review that and just let me know when you're ready to proceed.
A. Okay.
Q. So, in that paragraph, you state, and I'm paraphrasing, that Helsinn's scientists had proposed that palonosetron degrades to an oxo ---
A. Autooxidation.
Q. I'm sorry -- an autooxidation pathway; is that correct?
A. Yes.
Q. Could you tell me, what is autooxidation?
A. Hum. Auto, self, oxidation, right? So it's -- conventional wisdom on autooxidation is that a drug will undergo potential oxidation in the presence of oxygen, often triggered by an initiator of some kind.
And, that is, you've not added something intentionally to the system to cause the oxidation, okay? Other than reaction with oxygen.
But there may be other definitions of autooxidation.

Q. Do you --
A. Including in my own book.
THE COURT REPORTER: Including what?
THE WITNESS: Including in my own book.
Q. Do you recall whether at the time that you prepared this declaration and were told that Helsinn's scientists had proposed this autooxidation pathway, whether you had any reaction to that, hearing that?
A. I don't remember. The fact that I wrote this statement to me says I'm surprised.
Q. And when you say you were surprised, does that mean that you disagreed with that proposal?
A. No. I was just surprised.
Q. And your -- what was the basis for your being surprised?
A. It's exactly what I said here, is that -- as discussed above, neither of these observations would be obvious from the structure of the molecule which one would predict to be very stable and contain no -- not contain any functional groups that are normally associated with oxidative -- what I probably should have said there, is facile oxidative degradation but...
Q. So, again, your -- your statement that you were surprised was based on the structure of palonosetron, in your opinion, that it didn't have any of the features that would predict oxidative degradation?
A. Not in the hydrochloride form, yeah.

Q. Oxidation is a well-known chemical degradation pathway that is well known for pharmaceuticals?
A. It is a pathway that's there that we always -- we've got to be conscious of it.
Q. Are there specific ways of preventing oxidation in a formulation?
A. There are things that are done, but, again, it depends on the molecule and it depends on the observations that are made initially as to what process one might consider.
Q. Can we turn to Exhibit 163, which is your textbook, or the excerpts -- that contain the excerpts of your textbook? And if we could turn to Page 97.

On that page, do you see a section numbered 4 that's entitled "Inhibition of Oxidation"? Do you see that?
A. Yes.
Q. And then in that section, Dr. Stella, you list a number of ways of inhibiting oxidation, and those include exclusion of oxygen.

If you turn to the next page, "Alteration of Solution pH, Protection from Light," and then on the following page, "Use of Chelating Agents and Antioxidants." Do you see those, Dr. Stella?
A. Yes, I do.
Q. So, if someone was to predict, as a Helsinn scientist, that -- or a proposed Helsinn scientist that palonosetron was

undergoing oxidative degradation, couldn't they use the methods disclosed in your textbook that we've just gone through to address that oxidative degradation?

A. These are ways that are done, but each one of them has -- it also -- well, put it this way. Oxidation by itself is a complex mechanistic pathway. It determines -- it's affected by what triggers the oxidation. Oxygen access. Is oxygen access an important issue? What is the mechanism of the process? Are there more than one degradation pathway?

Very often with complex drug molecules, they're not single degradation pathways that are occurring. There are often multiple drug -- multiple degradation pathways that are occurring.

Without knowing that, one really would not know where to start in some ways, unless you do it purely empirically, and some people do that fairly empirically.

For example, as I point out in this chapter -- by the way, which I wrote.

Q. Okay.

A. So I'm the author of this chapter.

The -- for example, in very dilute solution, you cannot get rid of all oxygen. So if you've got a drug that's oxidatively sensitive, you know, head space displacement of air with nitrogen and things like that, really don't work very well because of the amount of dissolved oxygen in the water.

You're going to put it into a vial that's got a rubber stopper. The rubber stopper is permeable.

Now, I'm answering these questions as an expert in the field, not as someone just skilled in the art. Okay?

So you could read this, for example, an exclusion of oxygen, look at the example that I gave you with captopril, and say, well, for a dilute solution drug, it's not going to work. One's got to be pretty smart to put all that together. Okay?

So how someone -- what someone does, how they go about it, is pretty complex, you know. And so I -- to say that then people grind through these processes is not fair to -- it depends on the drug.

And it's my understanding that, you know, they thought there was autooxidation here, but, you know, based on my statement there, it was proposed to be. I -- you know, we don't know if there was or not. So, would you routinely go through that? No, I don't think you would routinely go through that.

Also, you don't want to put things into a formulation that are unnecessary. All right? So why put something into a formulation if it serves no purpose?

So, we are held in a very awkward regulatory environment as pharmaceutical scientists. And so it's a complex process, thought process, that you have to go through

to come up with the way to stabilize drug products.

Q. Let me just go back to your textbook here, and I hear everything you're saying.

My question, though, is: Doesn't this Section 4 of your book provide strategies for dealing with oxidation that might be seen in a formulation?

A. These are strategies. Whether they're applicable to a specific drug will depend on that drug, the dosage form that you're using, the delivery mechanism, the container you wish to use, what kind of rubber stopper you're going to use, are there initiators in the rubber stopper. There's so many things that are going here that, you know, we could spend hours literally going over that.

Q. So --

A. These are four processes that people might want to consider, but they're all dependent on the drug molecule, the properties of the drug molecule. And you're counterbalancing that with other formulation considerations such as concentration of drugs, the solubility of drug, other things that go into it.

So, it's a really fine balancing act that the pharmaceutical scientist has to go through.

Q. But these are for -- these are strategies that at least might serve as a starting point for addressing oxidation in a formulation?

A. These are four procedures that can be looked at under given circumstances, so...

Q. Okay. If we can just look at Page 99 of that section.

In there, you talk about the use of chelating agents and antioxidants. Do you see that?

A. Yes.

Q. My first question, I guess, for you is: Are you familiar with the use of chelating agents in pharmaceutical formulations?

A. Yes, I am.

Q. And is a chelating agent a common excipient that might be used in a pharmaceutical formulation?

A. It's not a common excipient. It's an excipient that's used, but it's not common.

Q. And could a chelating agent be used to address a autooxidation pathway?

A. If there is proof that metal ion catalysis triggers a reaction, but there's also -- there are also reactions where chelating agents interact with metal ions to actually catalyze oxidation breakdown. So one has to be very careful.

And there's also regulatory requirements.

For example, in Japan, if you're developing a product for worldwide usage, you basically stay away from, in this specific case, EDTA, because there is a -- there are some scientists in Japan that believe that EDTA is bad for you.

And so EDTA is something that can be looked at, if the conditions warrant it, but it's something that we really would like to stay away from, if we're producing a product that's going to be potentially used outside of Europe and the U.S.

Q. Well, let me just ask you a more basic question.

How does a chelating agent prevent oxidation?

A. It often doesn't, as I said, because I've got examples in my own work where it actually catalyzes oxidative degradation. So it's got to be due to the specific mechanism, related to the specific mechanism.

But in -- some oxidative reactions are triggered by metal ions. That's part of what we call the initiation part of the autooxidation process.

Q. Okay.

A. And metal ions can bind to metal ions and prevent that under some circumstances.

Q. So...

A. But they're usually used synergistically with an antioxidant. So it's very rare that you see EDTA used by itself.

THE COURT: Can we stop that for a second?

Q. So the chelating agent --

(Video stopped.)

THE COURT: I think maybe the witness misspoke there. He said, "Metal ions can bind to metal ions," and I think what

he meant was, "chelating agents can bind to metal ions."

MR. O'MALLEY: Yes, I agree.

MR. WONG: We agree, that's correct.

THE COURT: So we'll understand it as such. Let's go on.

(Video continued.)

Q. So the chelating agent, if I'm understanding your explanation, binds to metal ions in the formulation to prevent oxidation?

A. It -- metal -- chelating agents, such as EDTA, can bind with some metal ions, and fairly -- somewhat with a degree of specificity, but metal ions come from where? All right? I mean, we don't put metal ions into formulations. We have to know that the metal ions are, in fact, catalyzing reaction before you would use an EDTA, and what's the source of the metal ions? Do you normally just put nickel in a formulation? No, you don't do that. You don't put copper, you don't put iron in there.

So, those are part of the complications in developing formulations in that -- why are the metal ions in there to begin with, right? And you would only put an EDTA in if you, you know, had strong evidence that, in fact, metal chelation would have a positive effect on the stability.

Q. So, the chelating agent would -- strike that.

So, the effect of adding a chelating agent to a

formulation would be to achieve metal chelation; isn't that correct?

A. That's what it might be used for. Now, it may be that EDTA has other positive or negative benefits to -- that's why I'm confused.

Q. I wasn't talking about EDTA in particular. I was talking about a chelating agent.

A. Well, chelating agents are used to bind metal ions where metal ions are thought to be a problem. But you have to have reasonable support for that to include it.

Q. Right.

So the chelating agent will bind to metal ions in a formulation where there are metal ions present in that formulation?

A. Yeah. If -- they're capable of doing that, that's correct.

Q. And what do you mean by "capable of"?

A. Well, if there's metal ions there, certain metal ions.

For example, some of the chelating agents don't bind with sodium, potassium, but they will bind with some higher order metal ions. Depends on what contaminants are there, whether those -- and it will bind with those.

So if EDTA is present in the formulation, it will bind with metal ions, if they're there. But that doesn't mean that it's not there doing something else as well. I mean, we call

them -- EDTAs a chelating agent. We label it as that, or citric acid or some of the other components. But we don't know that they're -- that's what their purpose is in that particular formulation.

Q. Let me just ask you, if we turn to the next page of your textbook, Page 100, it states there in the -- I guess the second paragraph, towards the middle of the page, there's a statement, "Chelating agents act in an antioxidant capacity by binding metal ions, thus removing them, thermodynamically speaking, from the solution."

Do you agree with that statement, Dr. Stella?

A. They lower their activity -- they lower their thermodynamic activity, that's correct. Removing them is -- removing them, saying them, thermodynamically speaking, right? So it's an equilibrium. So you always have some free metal ions. You always have -- we understand that that's a dynamic process that's implied in that statement, yes.

Q. And as we've just been speaking at length about chelating agents, as you state, they're binding metal ions; isn't that correct?

A. Yes, they're capable of -- they're often designed to bind metal ions, but, for example, in the bottom here, we've got citric acid. It's a chelating agent, but it's also a buffer. So it may be playing multiple roles in a formulation.

Q. And we've spoken a little bit about an EDTA. Is EDTA a

common chelating agent in pharmaceutical formulations?
A. It's a -- it's a chelating agent that's used in some formulations.
Q. Okay. Maybe let me phrase it in terms of the way you wrote it here in your -- in your book.
Do you agree, Dr. Stella, that "The most effective chelating agents used pharmaceutically are EDTA, citric acid, many of the amino acids, phosphoric acid, and tartaric acid"?
A. Those are some that are used, yes, and they're the ones that I used in the capacity of a chelating agent, to different degrees.
Q. Okay. And among those that you have listed there, are EDTA and citric acid the two most useful agents?
A. That's what I state, but if you read the next paragraph, there's a qualifier in there.
"Their metal binding capacity is dependent on the state of ionization, both being most effective when their carboxylic acid groups are fully ionized. Thus, they lose their chelating capacity at low pH."
So, that general statement there is correct, but it is also very pH dependent.
Q. Okay.
A. So it depends on the pH of the solution as to whether they actually chelate metal ions.
Q. I'm going to mark another exhibit. DX 164.

Just take a minute to take a look at that exhibit, Dr. Stella. And, again, I apologize for the small typeface.

A. Yeah, I'm familiar with the book, obviously.

Q. So, Dr. Stella, this is a book entitled "Stability of Drugs and Dosage Forms;" isn't that correct?

A. That's the title of the book, yes.

Q. You're listed as an author, co-author of this book?

A. Yes, I am.

Q. And just can you confirm that this book is one of the books listed in Paragraph 6 of your declaration?

A. Assuming that Paragraph 6 is correct, the rest is correct.

Q. We've been talking about how dealing with a degradation of a -- of a pharmaceutical in a formulation, in your view, is a complex process. Isn't that correct?

A. Yes.

Q. Okay. If we can flip to Page 5 of your book, "Stability in Drugs and Dosage Forms."

A. Five pages or Page 5?

Q. Page 5.

A. Okay.

Q. And there's a section -- actually, it honestly starts on Page 4, Section 2.1, "Pathways of Chemical Degradation." Do you see that?

A. Um-hum.

Q. And there it talks about many and variable degradation pathways, if you look at the first sentence.

THE COURT: That word -- phrase is --

Q. And then it lists a number of --

(Video stopped.)

THE COURT: Again, just to correct the dep transcript, it says "many invariable," and the text of the book says "many and variable." So we'll understand it that way.

We can go on.

(Video continued.)

Q. ...section -- actually, it honestly starts on Page 4, Section 2.1, "Pathways of Chemical Degradation."

Do you see that?

A. Um-hum.

Q. And there it talks about many and variable degradation pathways, if you look at the first sentence.

A. Okay.

Q. And then it lists a number of potential pathways, which I believe are the same ones that you listed in your declaration.

A. You mean I plagiarized myself?

Q. No. In Paragraph 9.

A. Uh-huh.

Q. If -- the question I had for you actually is about a sentence you wrote in Paragraph 5 -- I mean, I'm sorry -- on

Page 5. And I will read that sentence into the -- into the record.

You state, "The immense chemical and pharmaceutical literature is probably underutilized as a source of such information."

My question for you is: Were you -- was that statement in -- that I just read in your book a suggestion to readers of your book that they should consult the immense chemical and pharmaceutical literature when facing a potential -- a chemical degradation issue in a -- in formulation development?

A. Well, I think what I've been saying in this whole book is that -- is that, while we could use the literature, there's -- drug molecules are complex. There's a quote, "Crap can happen." I could use another adjective, but "Crap can happen." So -- but I do, and I've taken the position that you should look for -- at the literature. So I'm not going to deny that. I mean, that's -- that's obviously something we should all do, right?

Whether I consulted the literature when I was doing the palonosetron, I don't know. Yeah, I don't remember.

Q. Dr. Stella, before the lunch break, we were talking about the statement in your book, which is the Stability of Drugs and Dosage Forms, and your statement in that about the use of vast scientific literature. Do you remember that?

A. Yes.

Q. I just want -- and I had asked you if you had looked at any literature in connection with the preparation of your declaration, and you said you didn't recall; is that correct?
A. That's correct, yes.
Q. Okay. There's -- on Page 145, there's a Section B, "Stability Protocols." Towards the middle of the page, you define six phases reflecting development -- the development of a new product, and I will just read those into the record:
"Preformulation, formulation development, proposed product, new product, established product, and revised product."
Did I read that correctly?
A. You've read them correctly.
Q. Do you agree, Dr. Stella, that the six phases of development that are listed there of the product are -- describe generally the process of formulation development?
A. These are the various phases that you have to go through. The complexity is that very often what came up in early phases of development, preformulation and early formulation development, often have to be significantly tweaked when products go out of specifications on storage.
So, the revised product at the end may or may not reflect, you know, what was done initially, just simply because of dosage requirements, safety issues, even problems found, you know, relatively late in the development phase.

So, you may think you've come up with a stable formulation during the formulation development, but you may find that on actual long-term storage, you know, everything goes to hell in a hand basket, and you have to do, you know, last-minute -- not last-minute, but late-version tweaking to get the formulation to work.

But, yes, these are generally the phases that you go through.

Today we probably use slightly different terminology from 1987 when this book was written. But it's -- it's -- it's -- I think it's '87, isn't it?

Q. Yes, I think that's correct.

A. '87.

Q. It's '86, actually.

A. '86, yeah. We probably use different terminology today, but the process would not be dissimilar.

Q. We're looking at Page 34. So the record is clear, we're looking at Exhibit 164.

There's a section there, 2.2, "Factors Affecting Chemical Stability."

Do you see that, Dr. Stella?

A. Yes.

Q. And I just had a question on the second paragraph. So, if you want to take a moment just to look at that.

A. Okay.

Q. It states in the second paragraph, "Factors determining the chemical stability of drug substances include intrinsic factors such as the molecular structure of the drug itself and environmental factors, such as temperature, pH, buffer species, ionic strength, light, oxygen, moisture, additives, and excipients."

Have I read that correctly, Dr. Stella?

A. You appear to have read it correctly.

Q. Dr. Stella, are those factors that I've just read factors that would have generally been known to a person working in formulation development?

A. One would -- one would know that these are all important variables and superimposed on all that is the container interactions issues that we also raised earlier.

Q. Okay. So, in addition to the container interaction issues, they -- a person working in formulation development would also be aware of the factors that I've -- that are listed here in your textbook?

A. These are the major ones that we are concerned with.

You know, for example, it didn't talk about metal ion contamination and things like that. So one would know that these were variables that we could -- that we would be concerned about, but we would also know that there were additional variables that, you know, are not so stated there.

Q. Let me try to ask it this way: If you could not predict

the degradation pathway, when you're trying to stabilize a drug, if you're having a hard time doing that, would you -- or if you're advising someone doing this, would you use the tools that are -- the strategies that are in your textbooks here to try to determine a way to stabilize it, and then figure out the degradation pathway afterwards?

A. Yeah. I -- I know where you're probably trying to go with the question. I don't quite understand your question.

For example, if you can't predict the stability -- well, we can't always predict the stability, you know. Even -- even with some data to back it up on.

So, would one try the particular strategies that are outlined in the book, right? Well, as I said earlier, it -- those are strategies that address -- or try to address a potential issue with an oxidative breakdown, for example. Okay? But, if you really don't know what really is happening here, how do you know that an oxidative -- or a strategy that prevents oxidative breakdown is really going to work if you don't know what's happening, right?

So, you really -- I don't know the whole history of the development of this drug. You know, I've not been privy to the process that went through the minds of the researchers here.

All my declaration is saying, basically, is that the whole process, the strategy that you might develop

empirically, logically, routinely, whatever, none of that really makes sense, and you have to really often cater what you're going to do to the individual drug.

That's where the really successful companies are, is they -- they have a -- not a good scientific basis, but they analyze data properly. You know, they look at observations and draw conclusions, et cetera. That -- that process of how you go down that road is very complex, and it's very much driven by the creativity of the group doing the work.

And so, you know, I was once asked, well, isn't what you're doing a routine, you know, decision-making tree? I said, yeah, it's a Stella tree. You know, it's me as an inventor going down that line. It is not necessarily one that someone skilled in the art would go down.

And so, as an inventor, you look at -- you know, you hope what you have as an inventor is someone that can make astute observations, critical decisions, and comes up with something that -- a unique set of observations and formulations that work, right? And that's part of the issue of creativity. That's part of the component of the patent.

I'm not saying that's what went on here. I don't know the process. But all I can say is that that process for most drugs is not routine. Whether all of those processes are patentable, et cetera, I'm not going to draw that conclusion. That's not my job. You know, that's the job of the lawyers

and the Patent Office and the judges to make that judgment.

(Video of Valentino J. Stella concluded.)

MR. ASHKENAZI: Your Honor, that's the end of this deposition. We have another 17-minute deposition video if, Your Honor, we have time, we can play now.

THE COURT: What's -- what's your preference, counsel?

MR. LOMBARDI: We have no objection to playing it now.

THE COURT: Okay.

MR. ASHKENAZI: So this is the deposition video of Dr. -- excuse me -- Dr. Navin Vaya. Dr. Navin Vaya was a 30(b)(6) witness on behalf of DRL. Dr. Vaya is DRL's project manager for its generic palonosetron formulation. And his testimony addresses DRL's ANDA and issues relating to objective indicia of nonobviousness, including copying.

THE COURT: I'll be right with you.

MR. ASHKENAZI: Umm.

THE COURT: Yes?

MR. ASHKENAZI: DRL -- do we need to -- is there anything confidential that you'd like to --

MR. SENDER: Yes.

Your Honor, in this particular deposition, there are a few things that might be confidential under the protective order, and so we would ordinarily ask that this part of the

transcript be sealed until we have a chance to see exactly what is in here.

THE COURT: We can seal the courtroom for purposes of screening this video, and it will consist of a temporary filing under seal of this portion of the trial.

MR. SENDER: Thank you, Your Honor.

MR. ASHKENAZI: Thank you, Your Honor.

THE COURT: Mr. Sender, if you would, please, give me a sealing -- a proposed form of sealing order that simply refers to this portion of today's transcript.

MR. SENDER: We shall do that, Your Honor.

THE COURT: And that will make it neat so that before the transcript is filed on the docket, the sealing order will take care of providing a redacted version for -- a redacted and an unredacted version. The redacted version would be what somebody could get ahold of under our usual rules, and the unredacted version would remain under seal until further order of the Court.

Okay. Just let me finish my notes, and then I'll be with you.

And, counsel, would you please attend to clearing the courtroom, however should it be done.

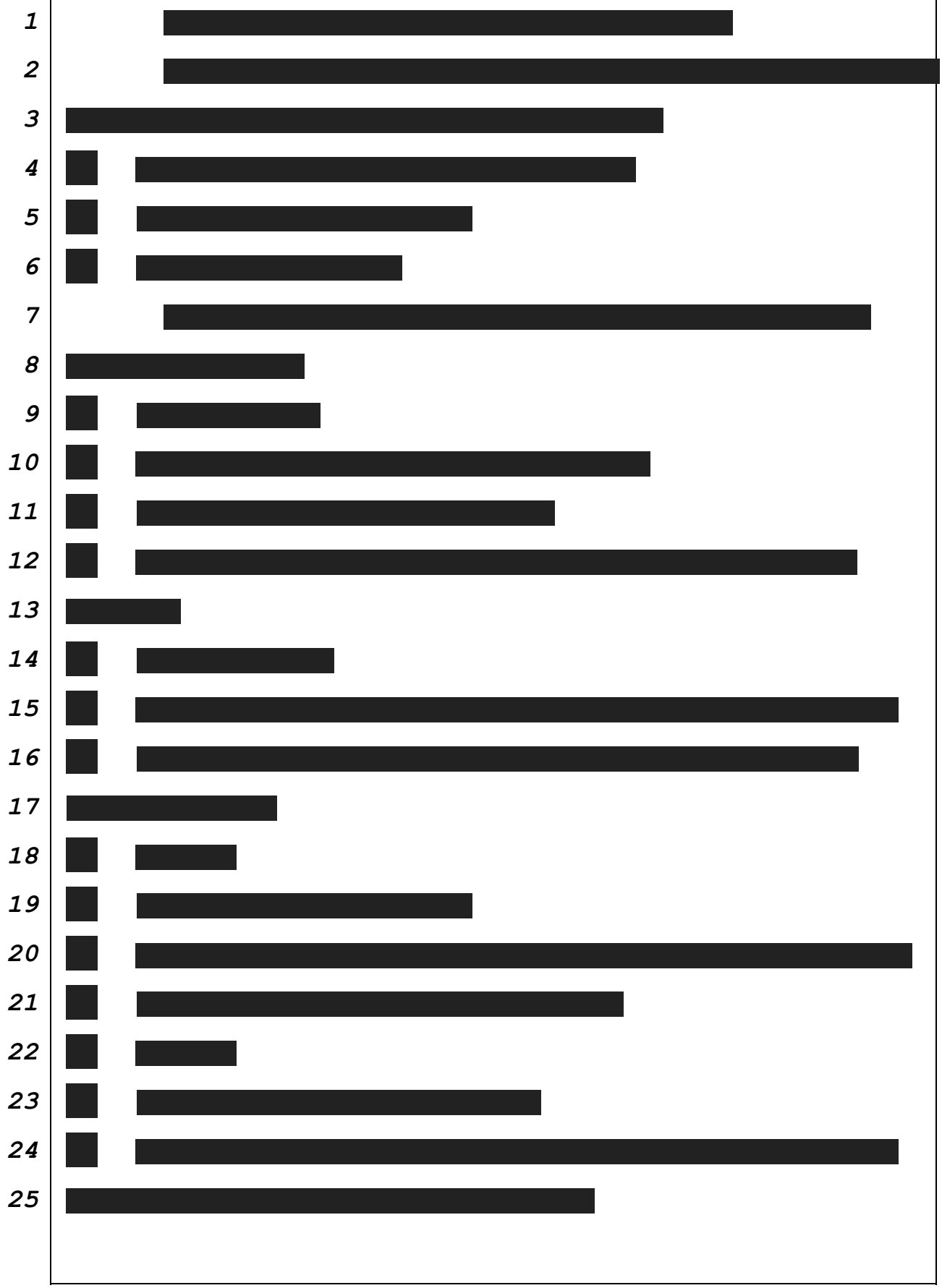
MR. SENDER: I believe that's it, Your Honor.

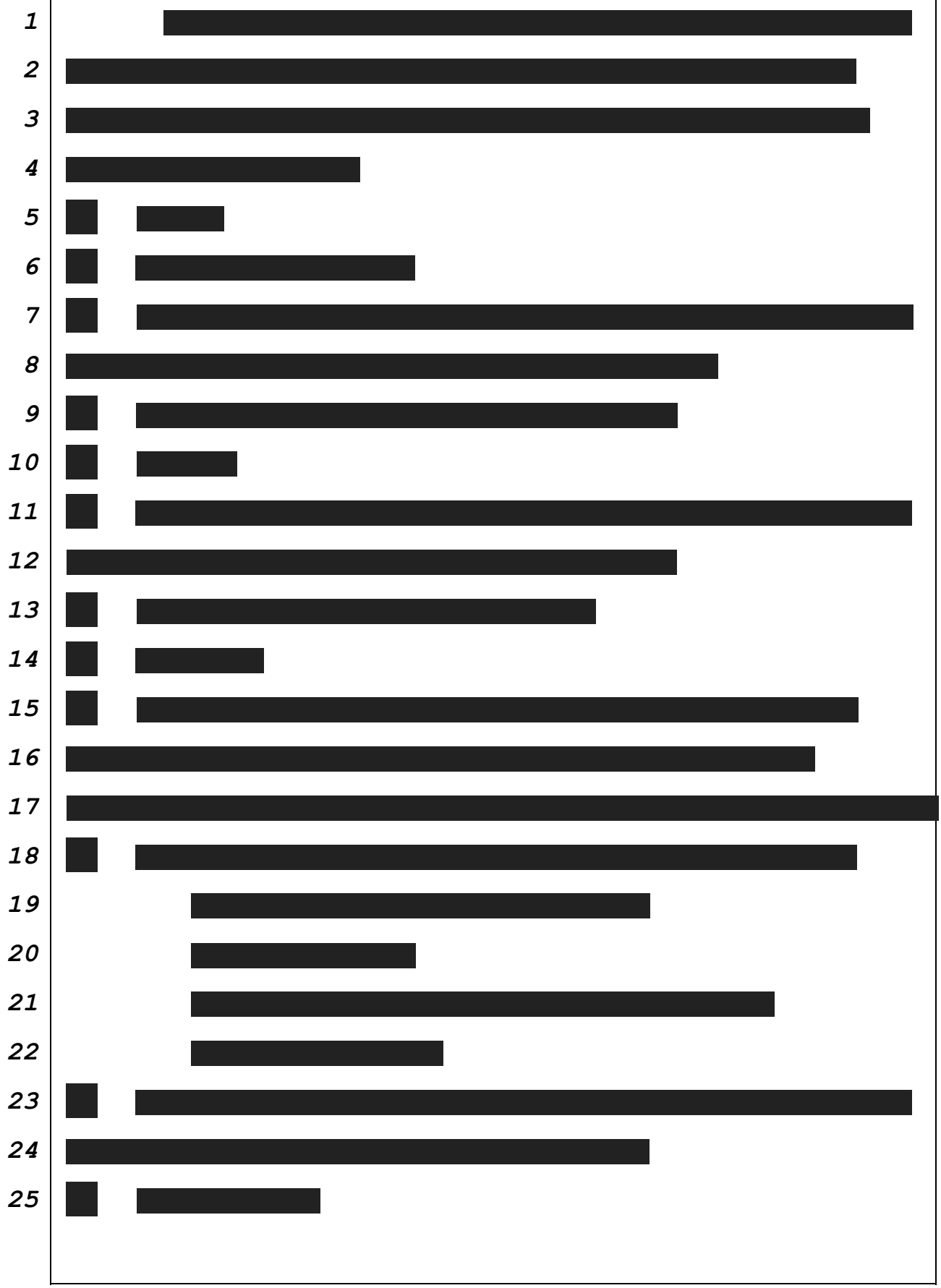
THE COURT: Okay. Then we're ready. Thank you.

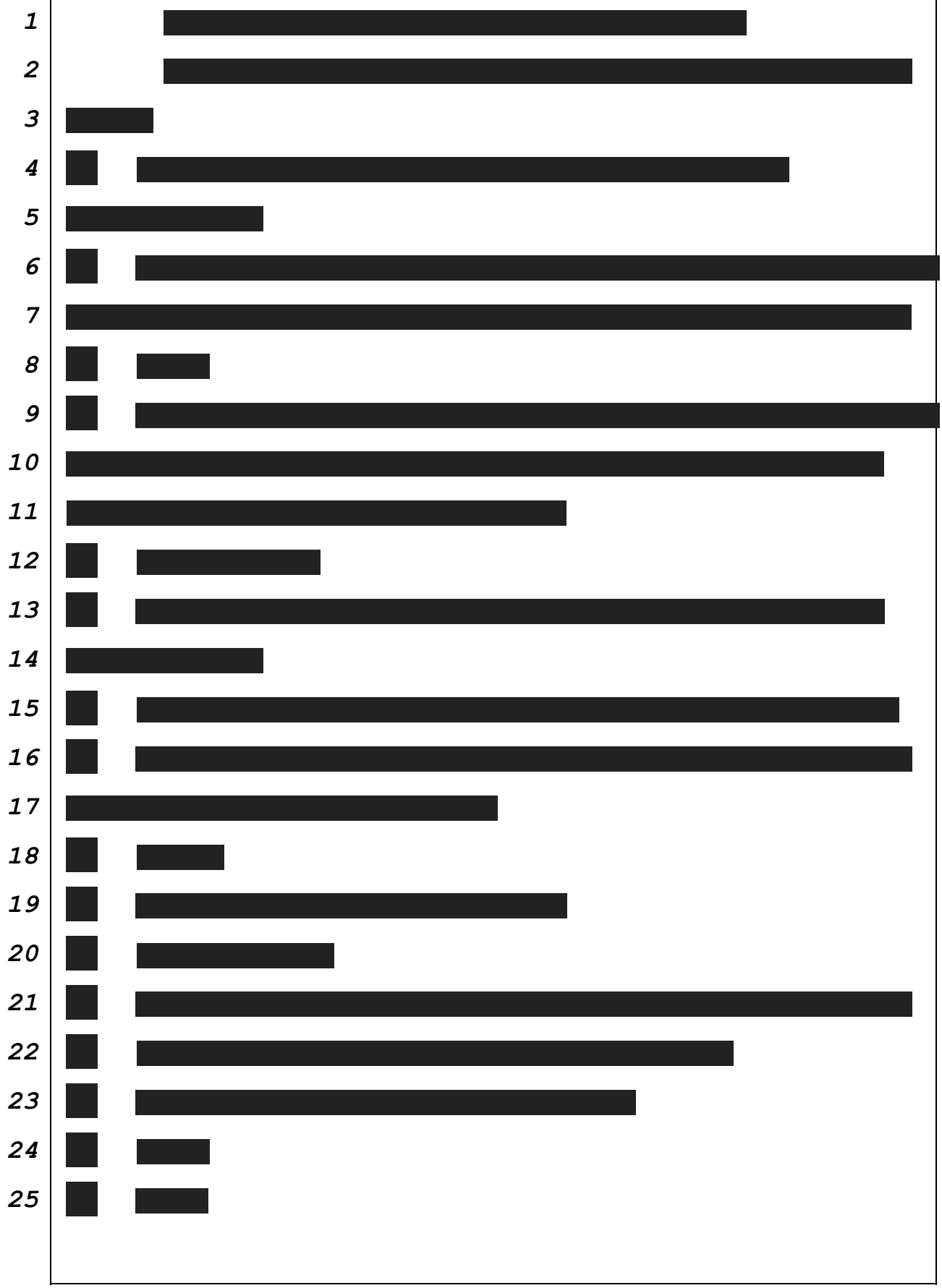
(By order of the Court, the proceeding was sealed from this

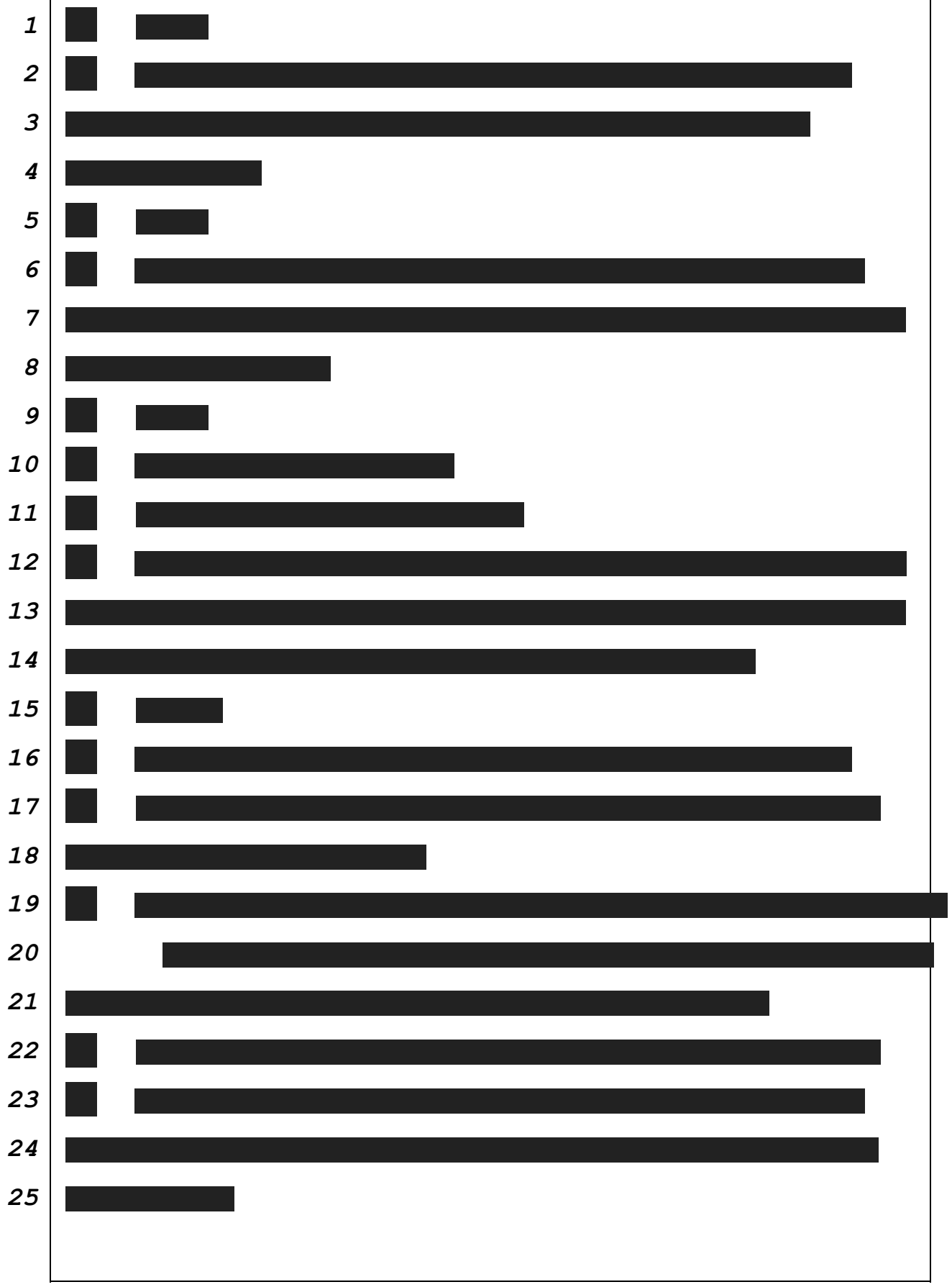
point.)

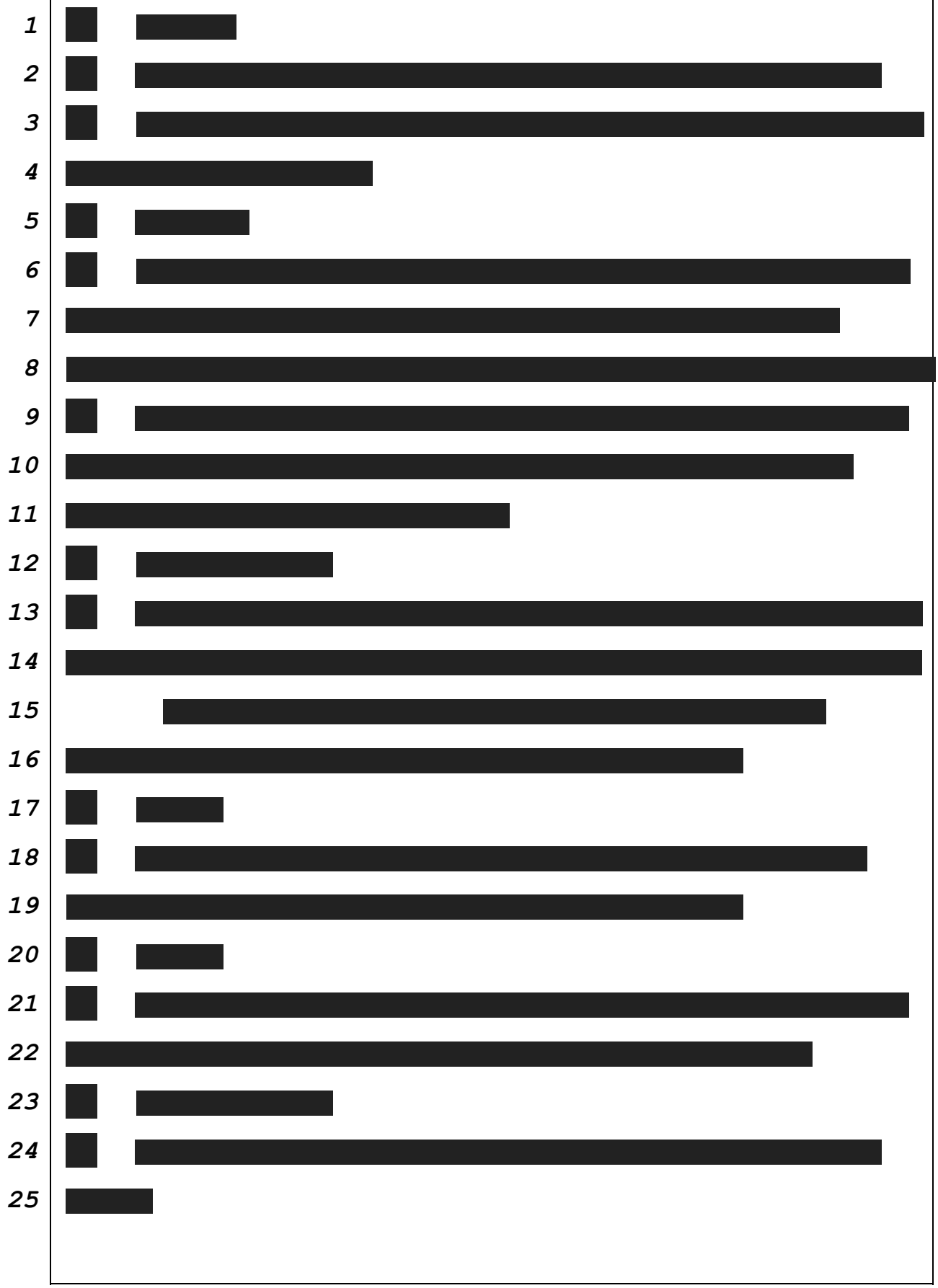
(The video testimony of Navin Vaya was played.)











(The video testimony of Navin Vaya was concluded.)

MR. ASHKENAZI: Your Honor, that's the end of this deposition video. Can we have -- it maybe a good time to take a lunch break, I think.

THE COURT: That's fine. What will we do this afternoon?

MR. ASHKENAZI: We -- I think we have one more video

and then Dr. Amidon will be taking the stand.

THE COURT: Okay. Fine. Shall we resume at 1?

MR. ASHKENAZI: That sounds good, Your Honor.

(Luncheon break taken at 12:13 p.m.)

THE COURT: Okay. Go right ahead, counsel.

MR. ASHKENAZI: So, your Honor, just to preview where we stand for the next day and-a-half or so, we plan right now on playing Ms. Limor Zahavi's deposition video which should run about 43 minutes or so, Your Honor.

Afterwards, Dr. Gordon Amidon will take the stand for plaintiffs. And then following that sometime tomorrow, we will be playing Dr. DeLuca's deposition designations. Just so your Honor is aware right now, the parties are still negotiating. Plaintiffs have cut their portion down to about 12 to 15 minutes or so, but with the excessive designations, which we're still negotiating, it may be close to an hour from defendants.

THE COURT: That's fine.

MR. ASHKENAZI: With that, we'll play now Ms. Limor Zahavi's deposition video. Ms. Limor Zahavi was a 30(b)(6) witness on behalf of Teva. Ms. Zahavi is the head of the development for nasal and sterile products at Teva, and her testimony addresses Teva's ANDA and issues relating to objective indicia of nonobviousness, including copying.

THE COURT: How do you spell her name, please?

MR. ASHKENAZI: First name is L-I-M, as in Mary, O-R. Zahavi, Z-A-H-A-V-I.

THE COURT: I'll be right with you.

And this deposition was taken for purposes of trial; is that correct?

MR. ASHKENAZI: Yes, your Honor.

THE COURT: So, it's a trial deposition?

MR. LOMBARDI: It was a 30(b)(6) deposition of one of our witnesses, and they are entitled to play it at trial. We have no -- no objection.

THE COURT: Fine. Okay. Anybody need a sealing order on any of this?

MR. LOMBARDI: Yes, your Honor. This is a Teva witness who's in a very similar position as the last witness we dealt with, so we would ask for the same arrangements as were made for the last deposition, if we could.

THE COURT: I direct that this portion of the trial be placed under temporary seal, and if someone would submit to me an order for that purpose.

MR. LOMBARDI: We will, your Honor.

THE COURT: Okay. Thank you. And counsel are responsible for making sure the courtroom is properly sealed. And we can proceed.

MR. ASHKENAZI: Okay, your Honor?

THE COURT: So, this is about 45 minutes?

MR. ASHKENAZI: Yes.

THE COURT: Okay. Fine.

MR. ASHKENAZI: And if I may just for the record identify some exhibits --

THE COURT: Sure.

MR. ASHKENAZI: -- that will be used, and, again, they're in the binder, I believe, that we have provided the Court.

Zahavi Deposition Exhibit 19 corresponds with DTX-0131.

Zahavi Deposition Exhibit 20 corresponds to DTX-0132.

Zahavi Deposition Exhibit 21 corresponds to DTX-0133.

Zahavi Deposition Exhibit 22 corresponds with DTX-0134.

Zahavi Deposition Exhibit 30 corresponds to DTX-0142.

Zahavi Deposition Exhibit 34 corresponds with DTX-0146.

Zahavi Deposition Exhibit 38 corresponds with DTX-0150.

Zahavi Deposition Exhibit 40 corresponds with DTX-0152.

And Zahavi Deposition Exhibit 53 corresponds with DTX-0165.

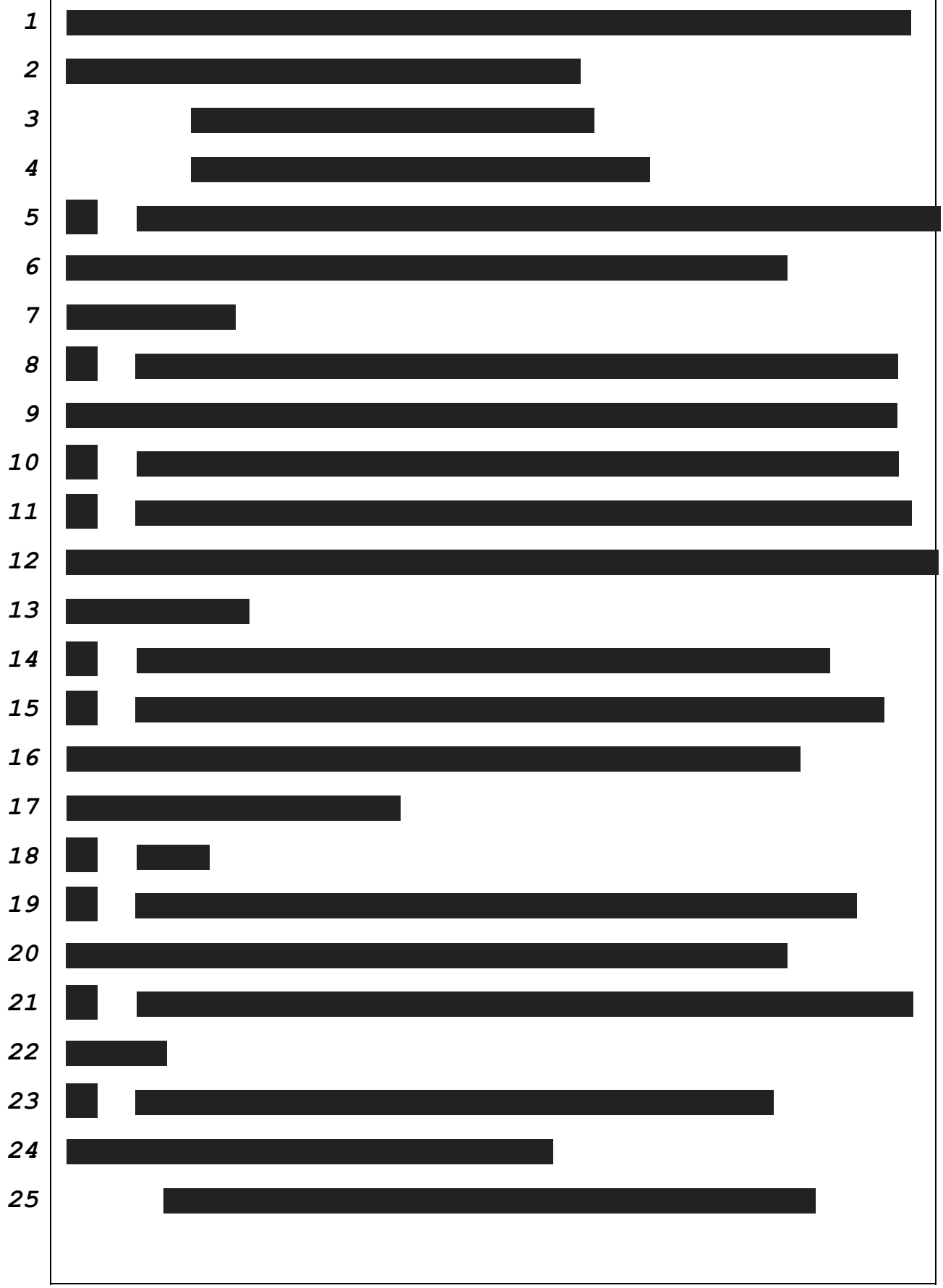
Thank you, your Honor.

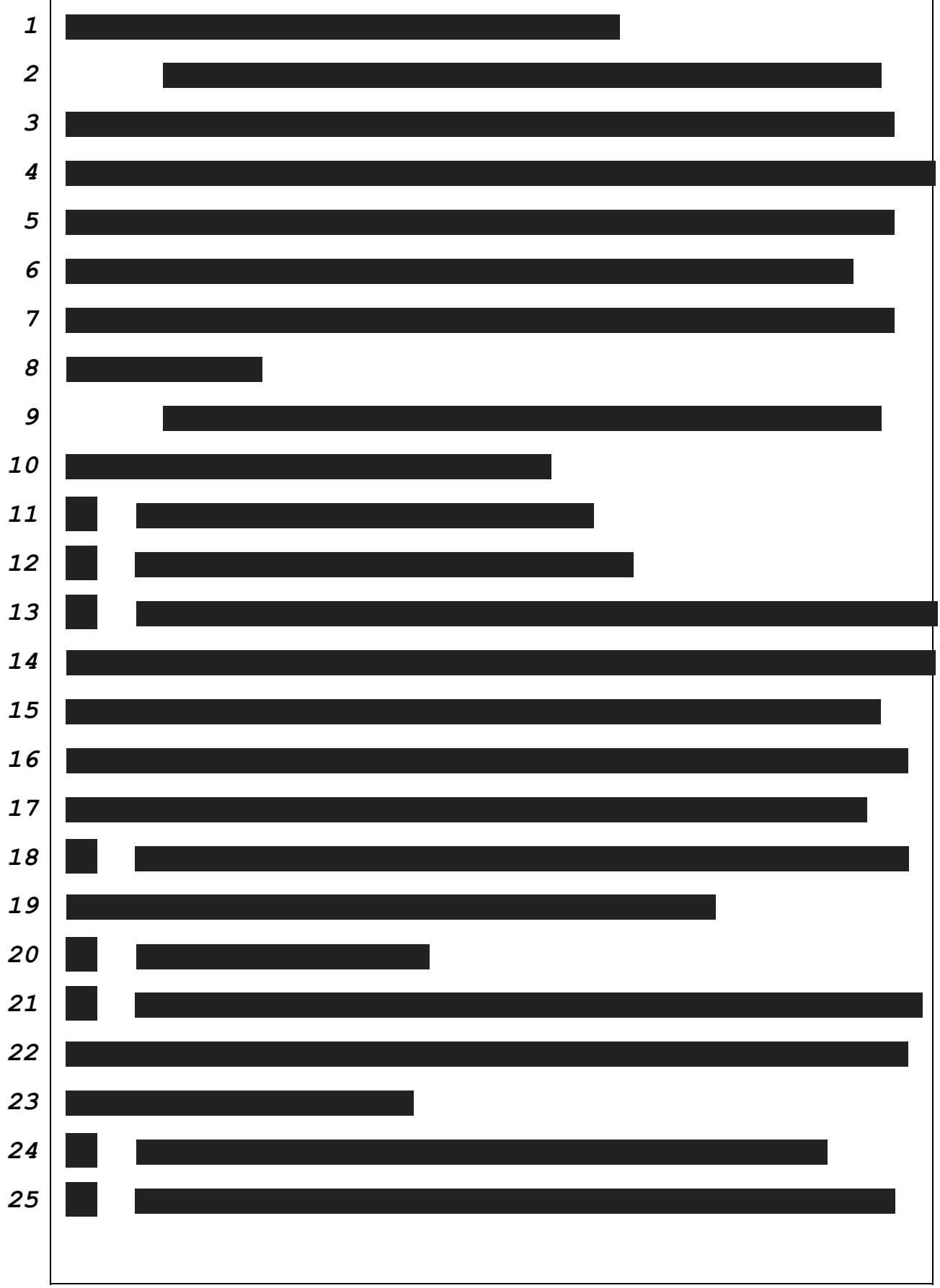
THE COURT: Okay.

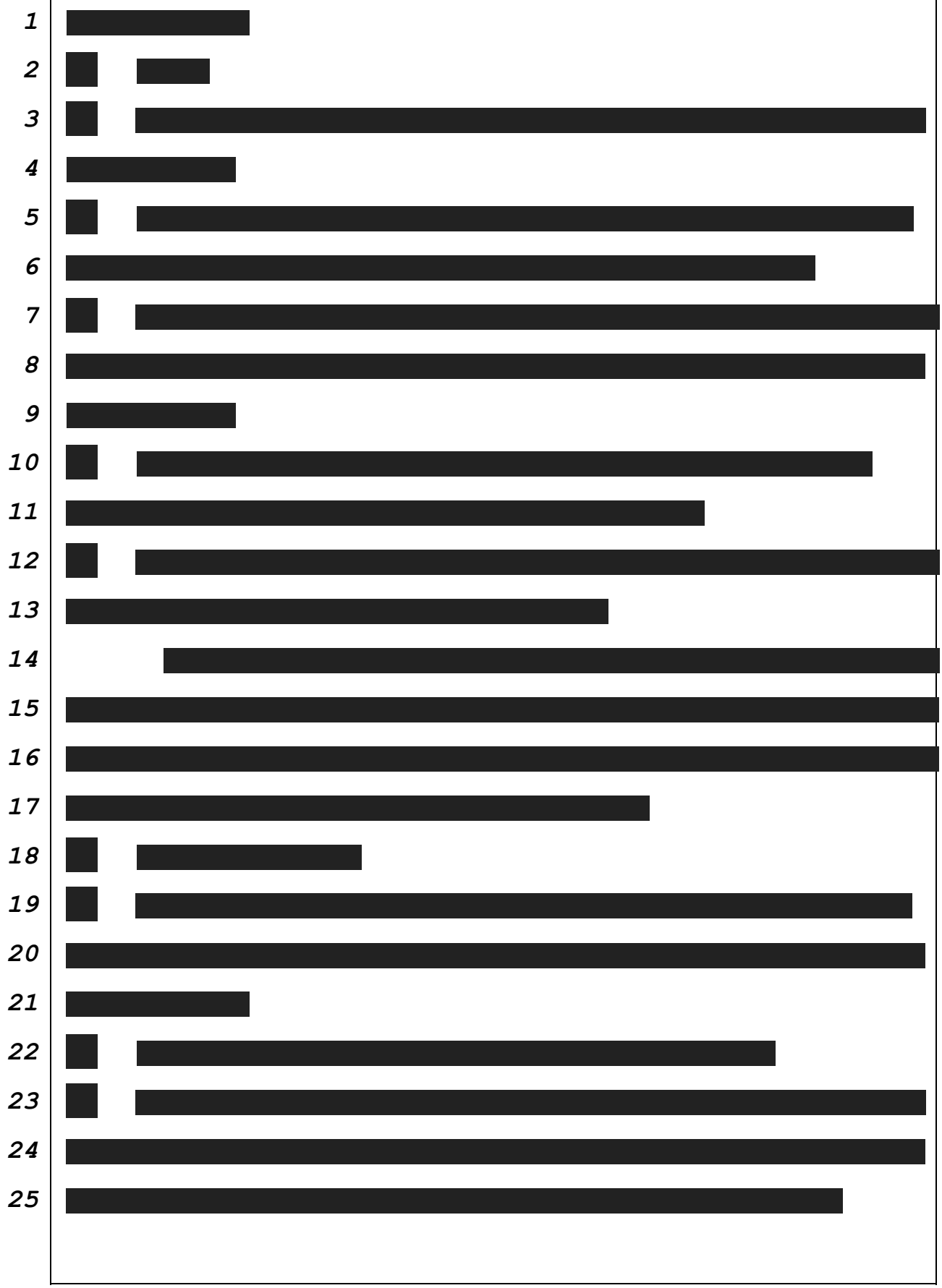
(By order of the Court, the proceeding was sealed from this point.)

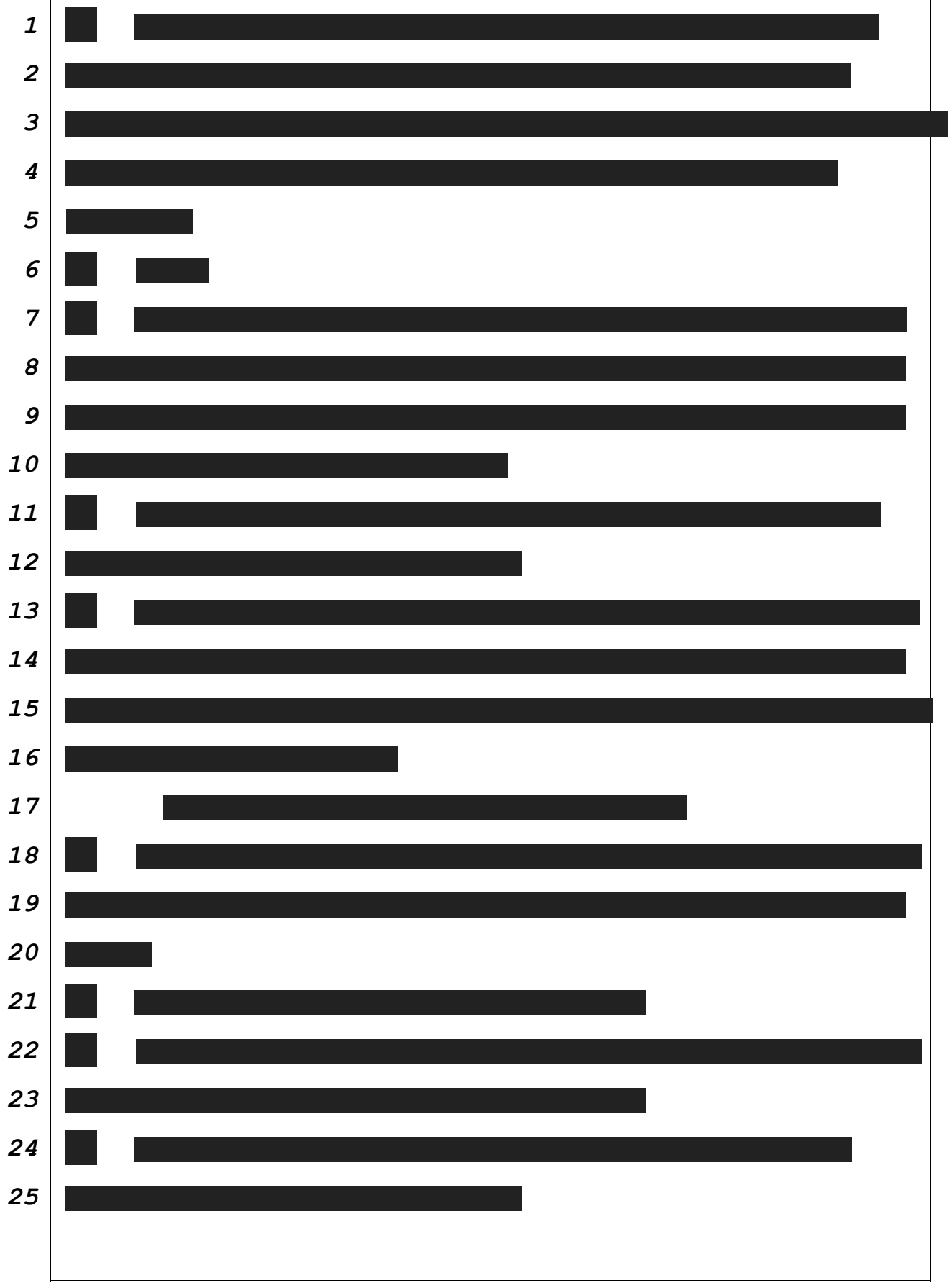
(Video deposition of Limor Zahavi played as follows:)

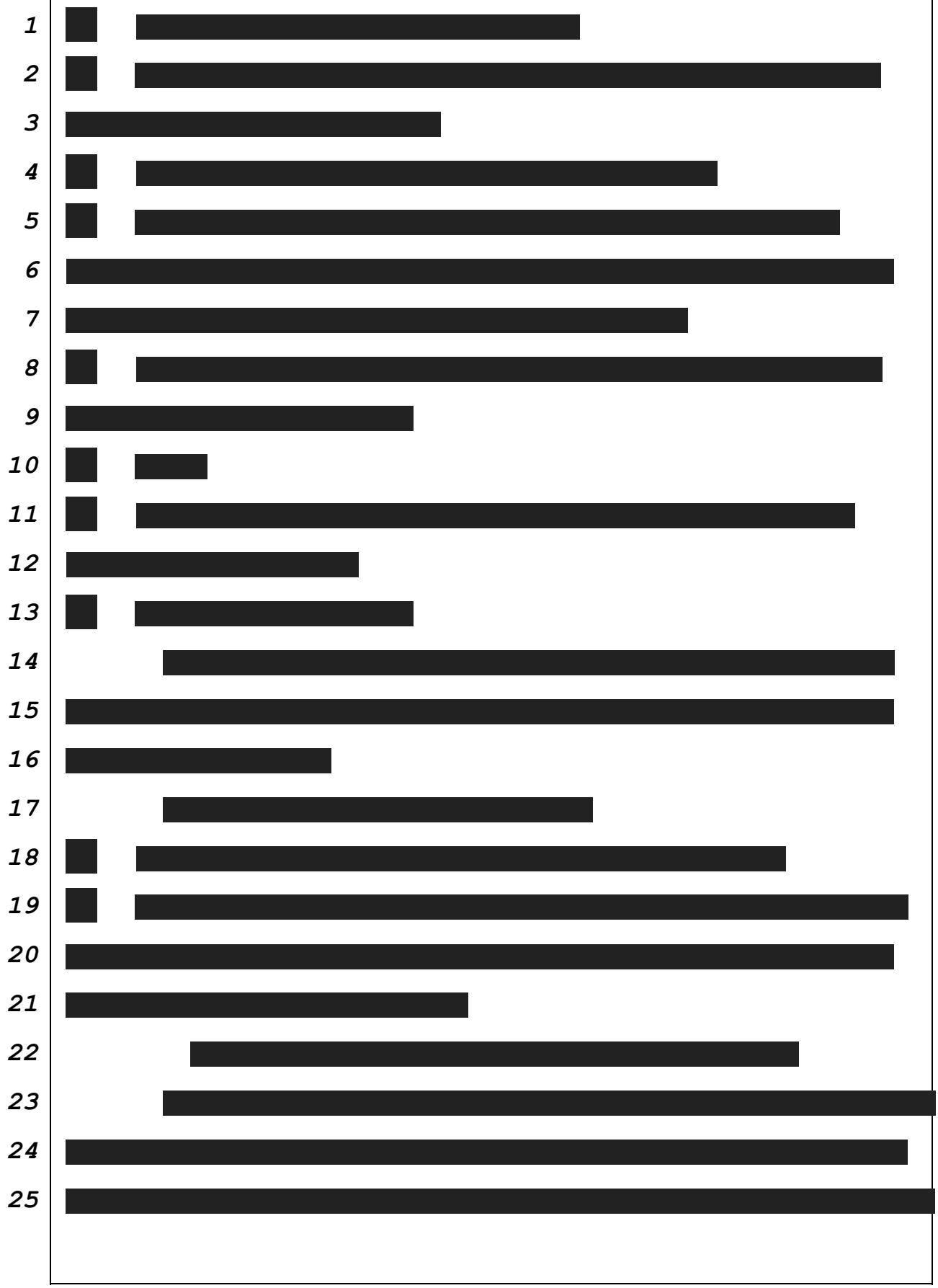
[redacted]

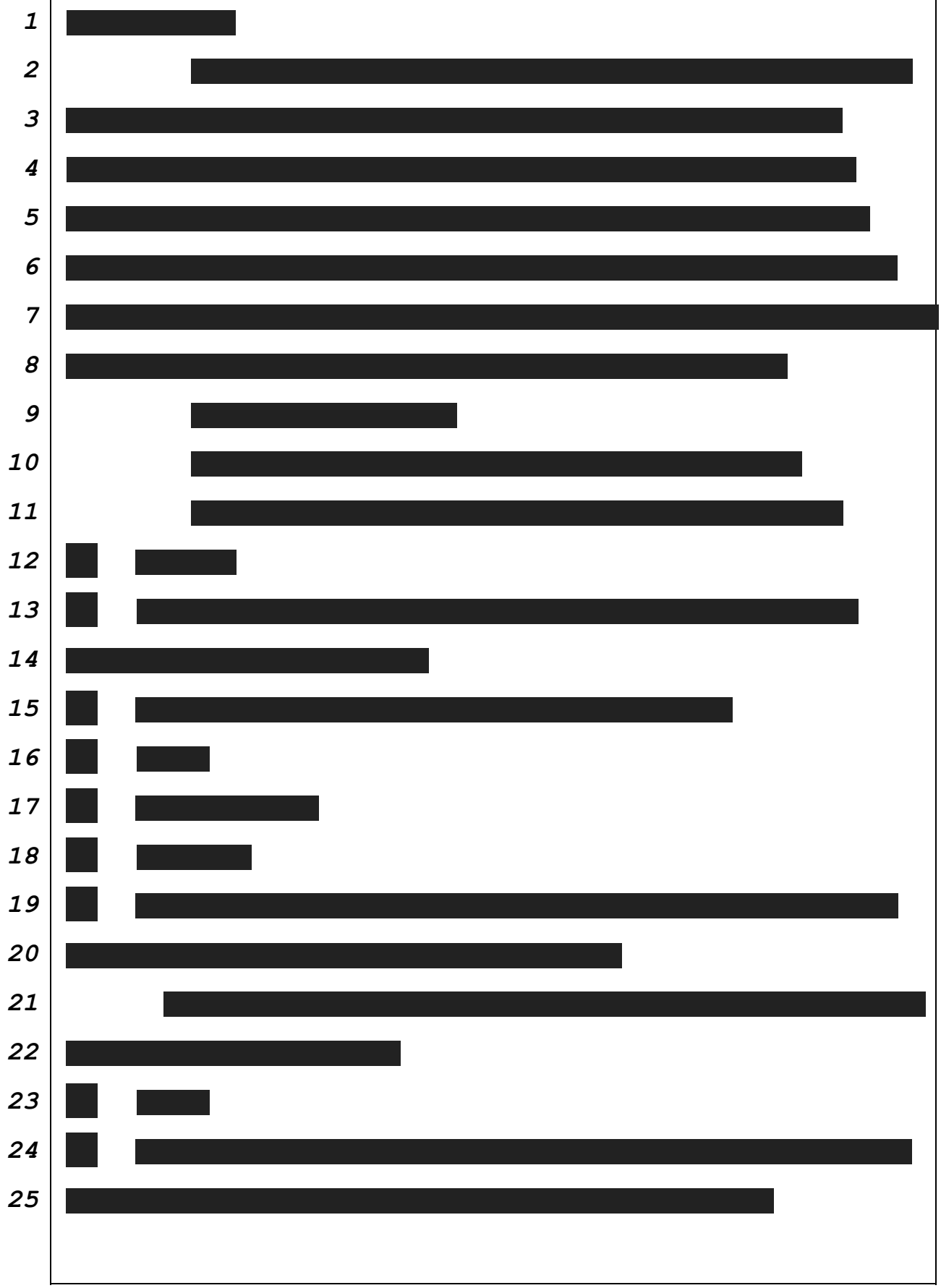


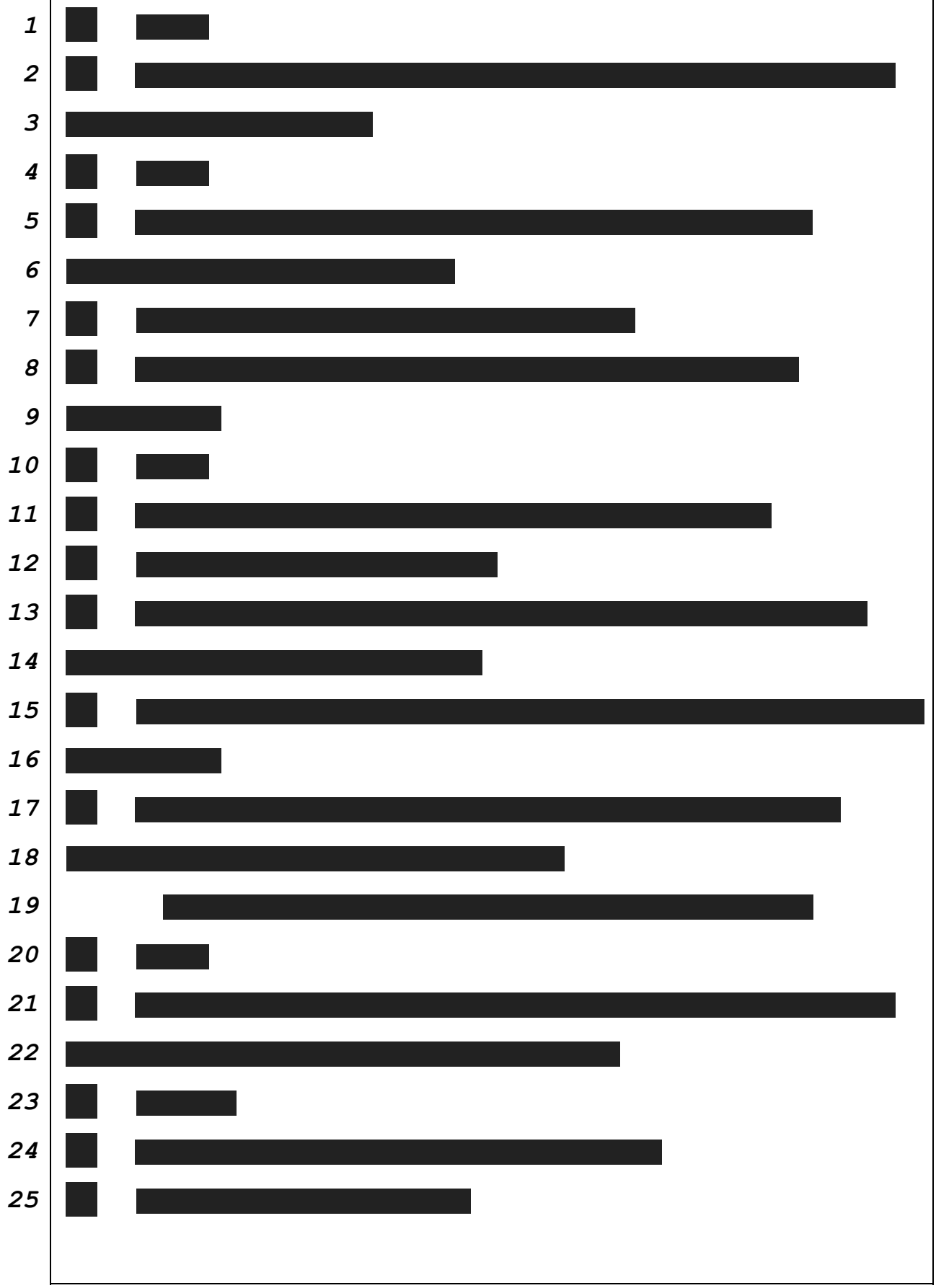


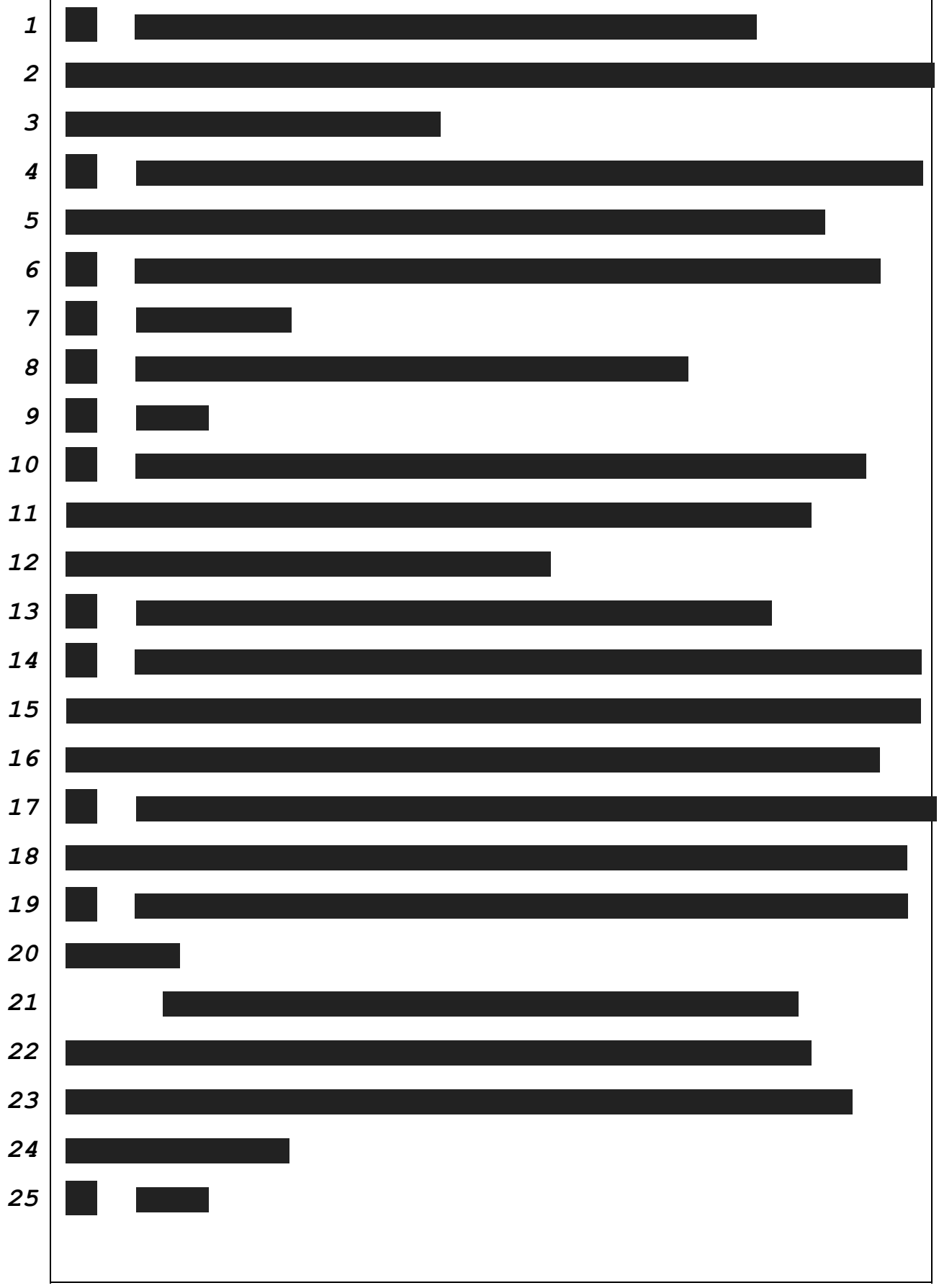


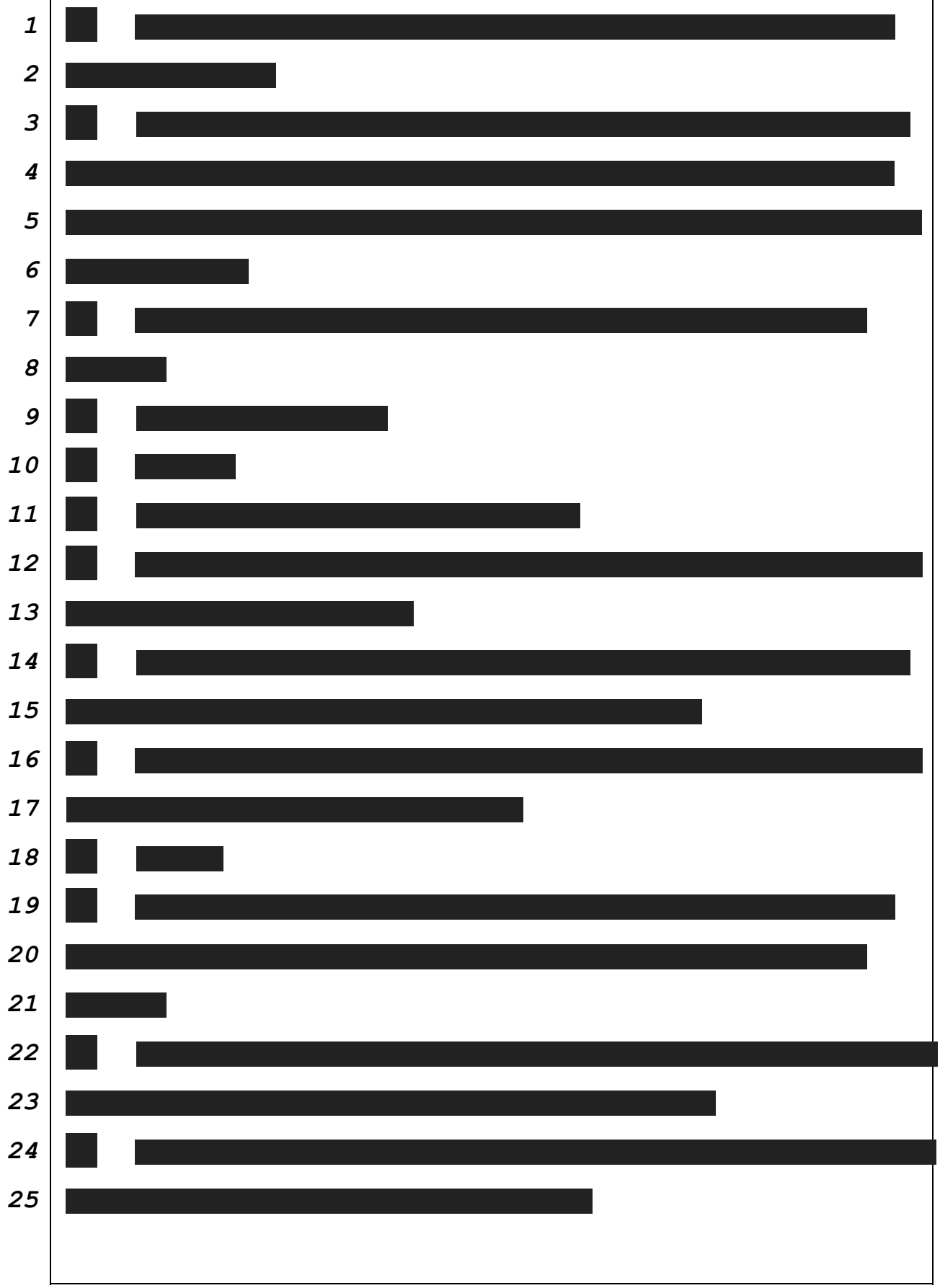


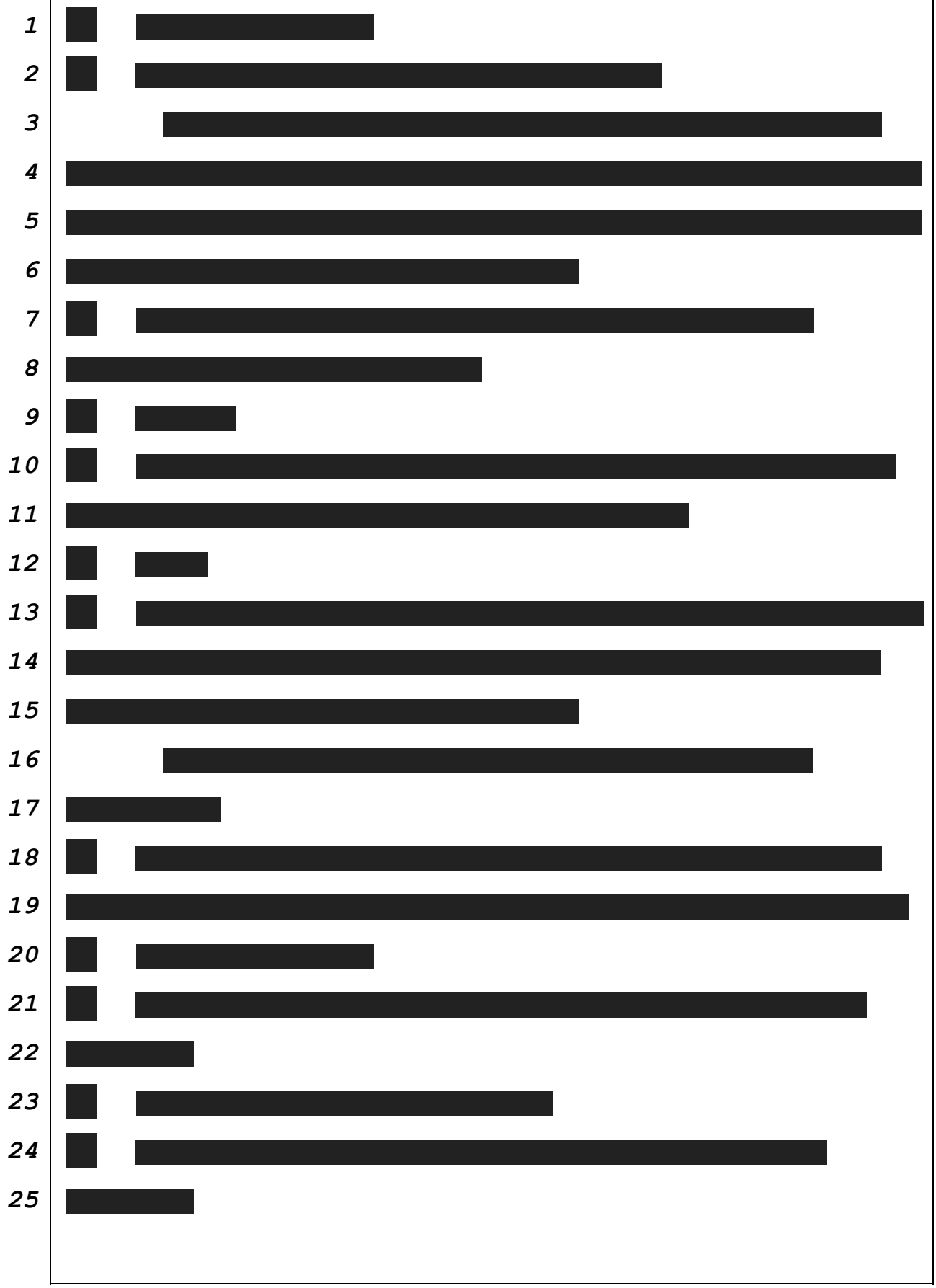


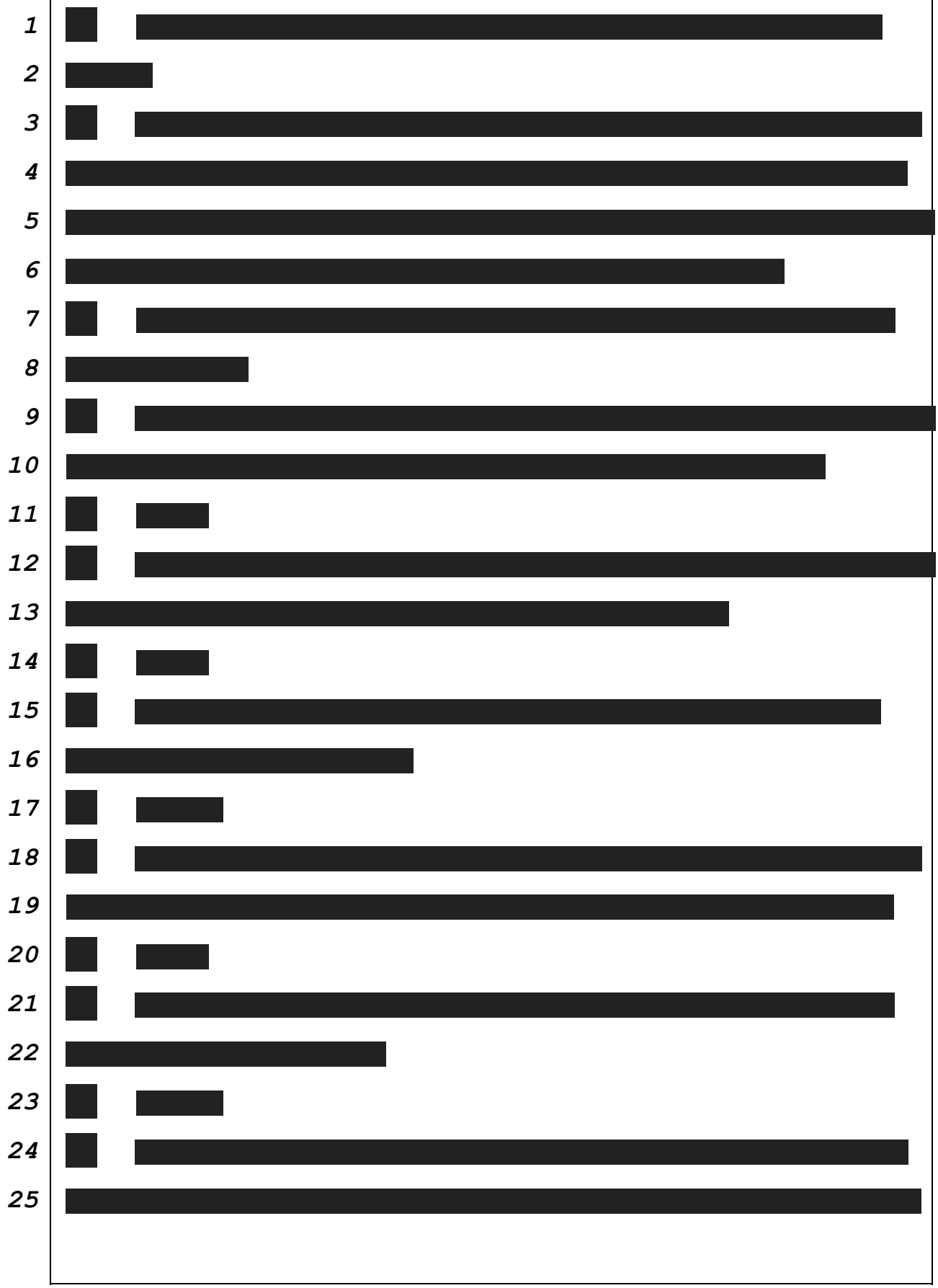


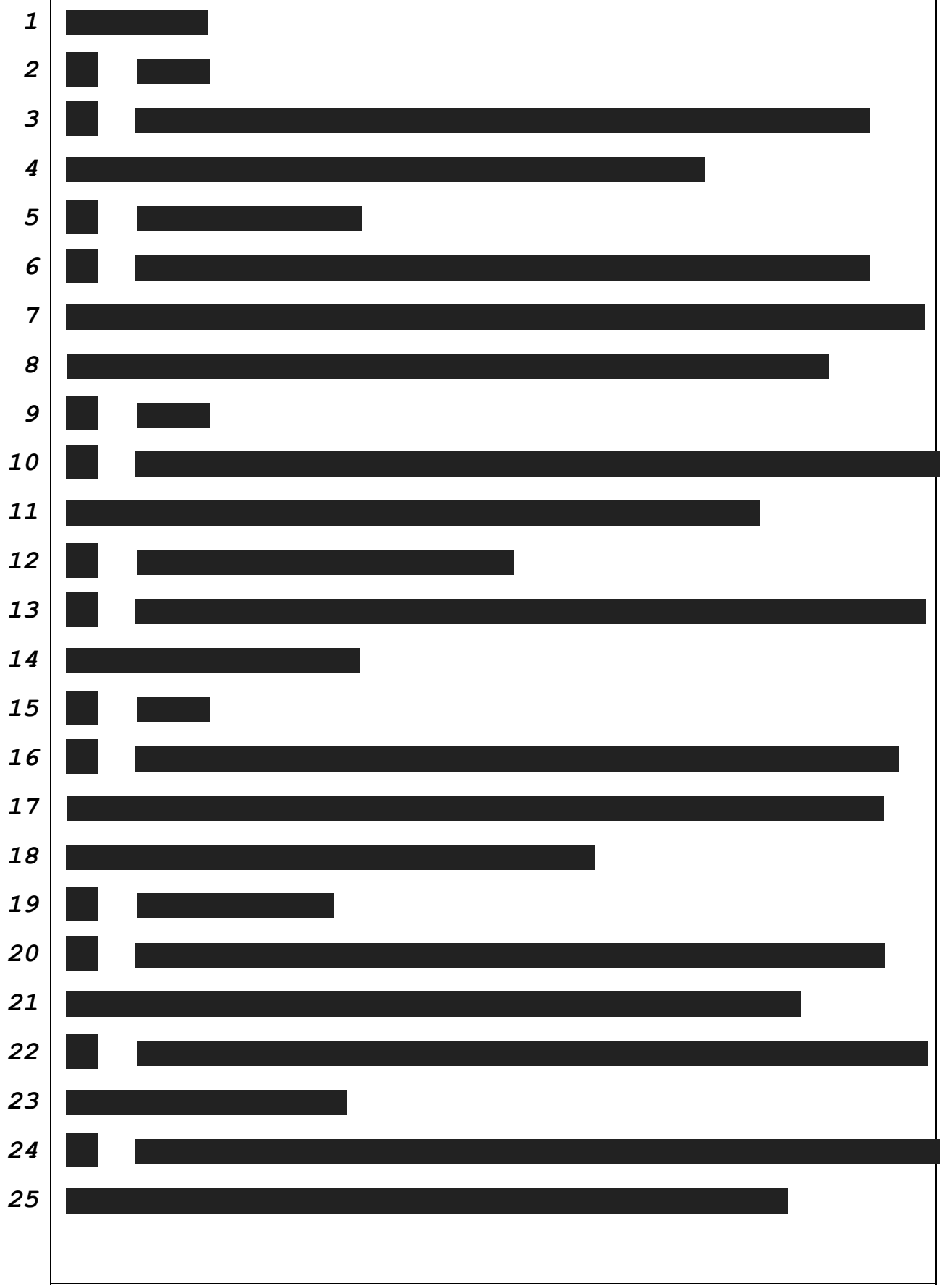


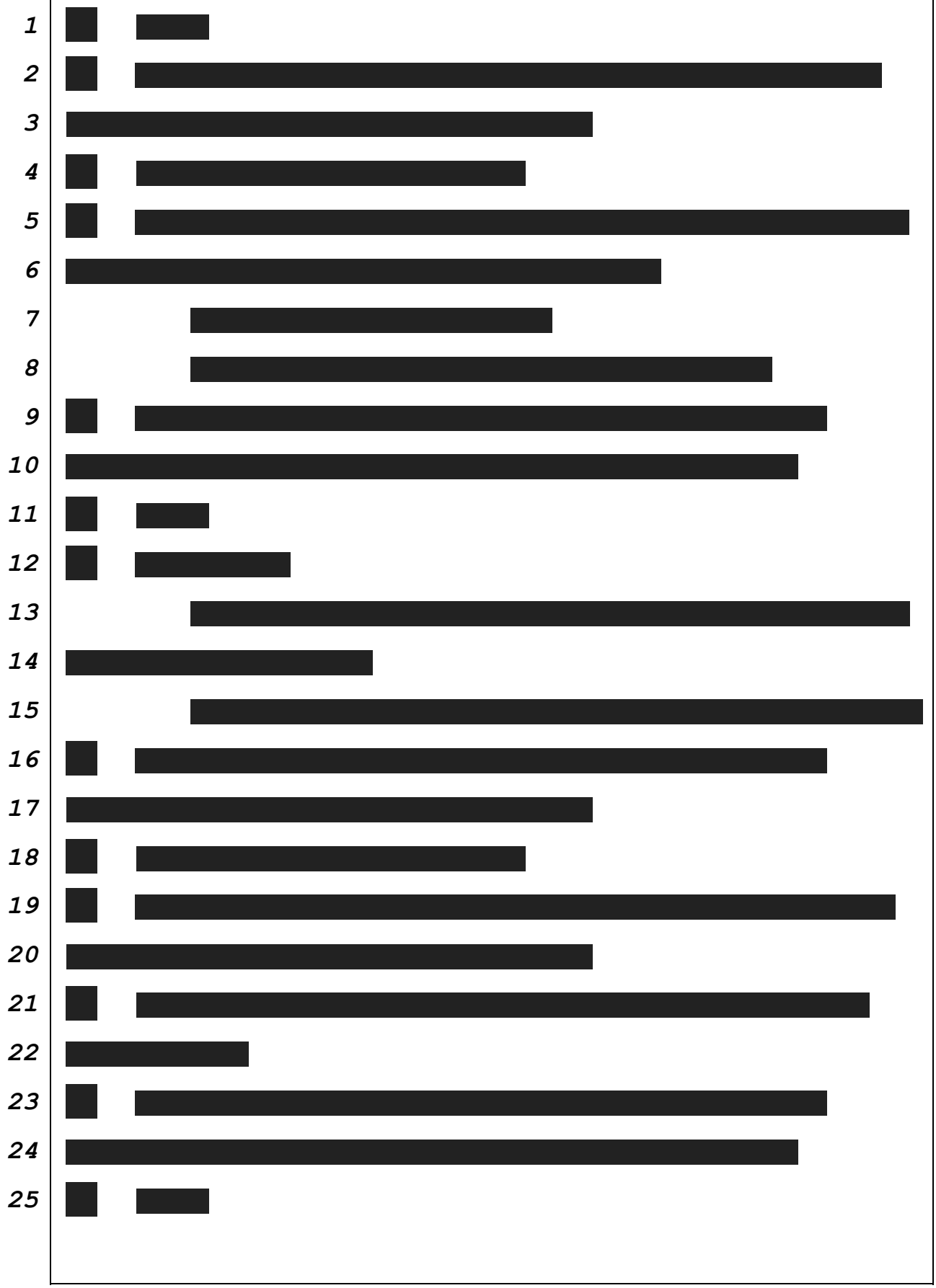


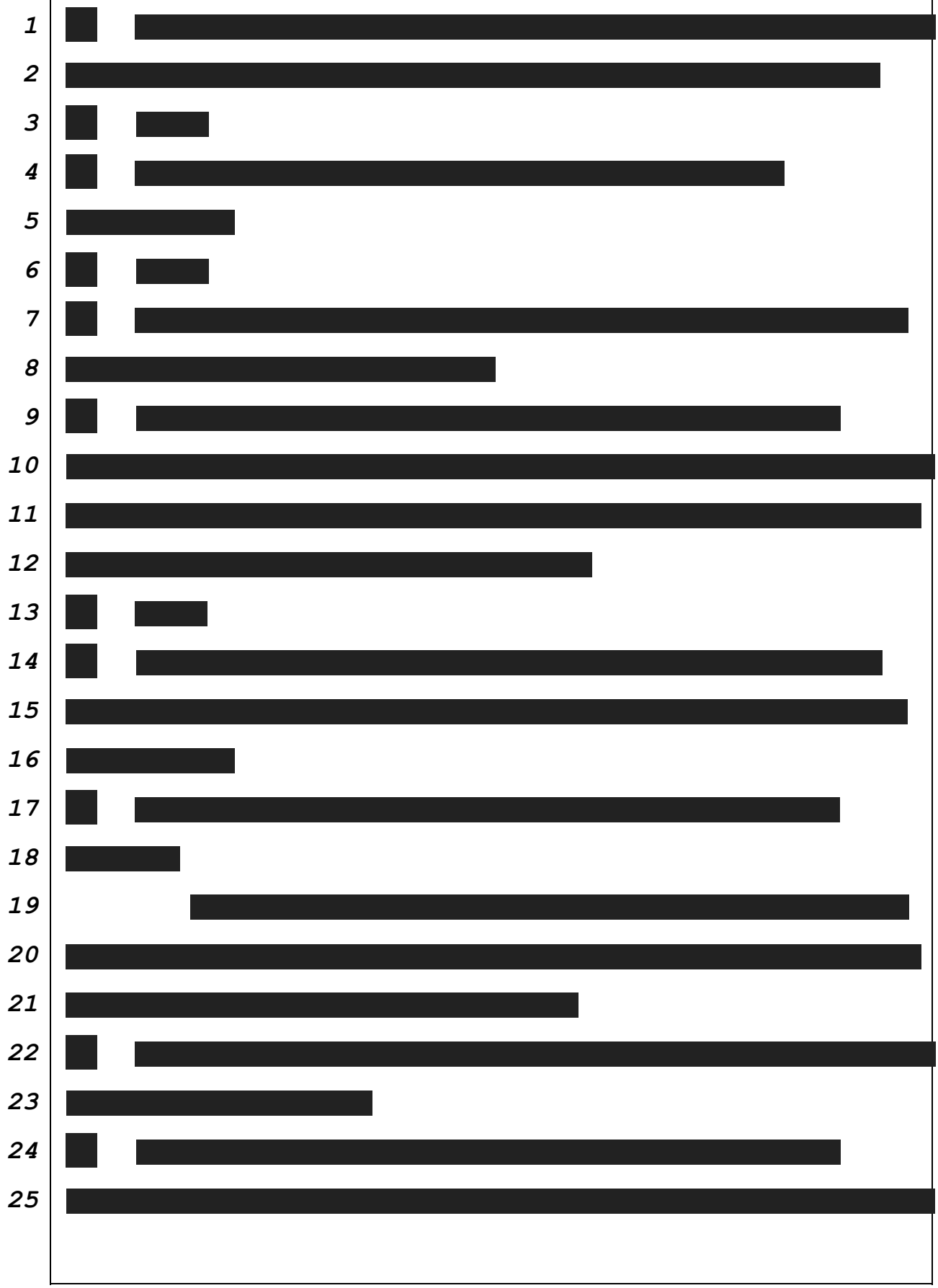


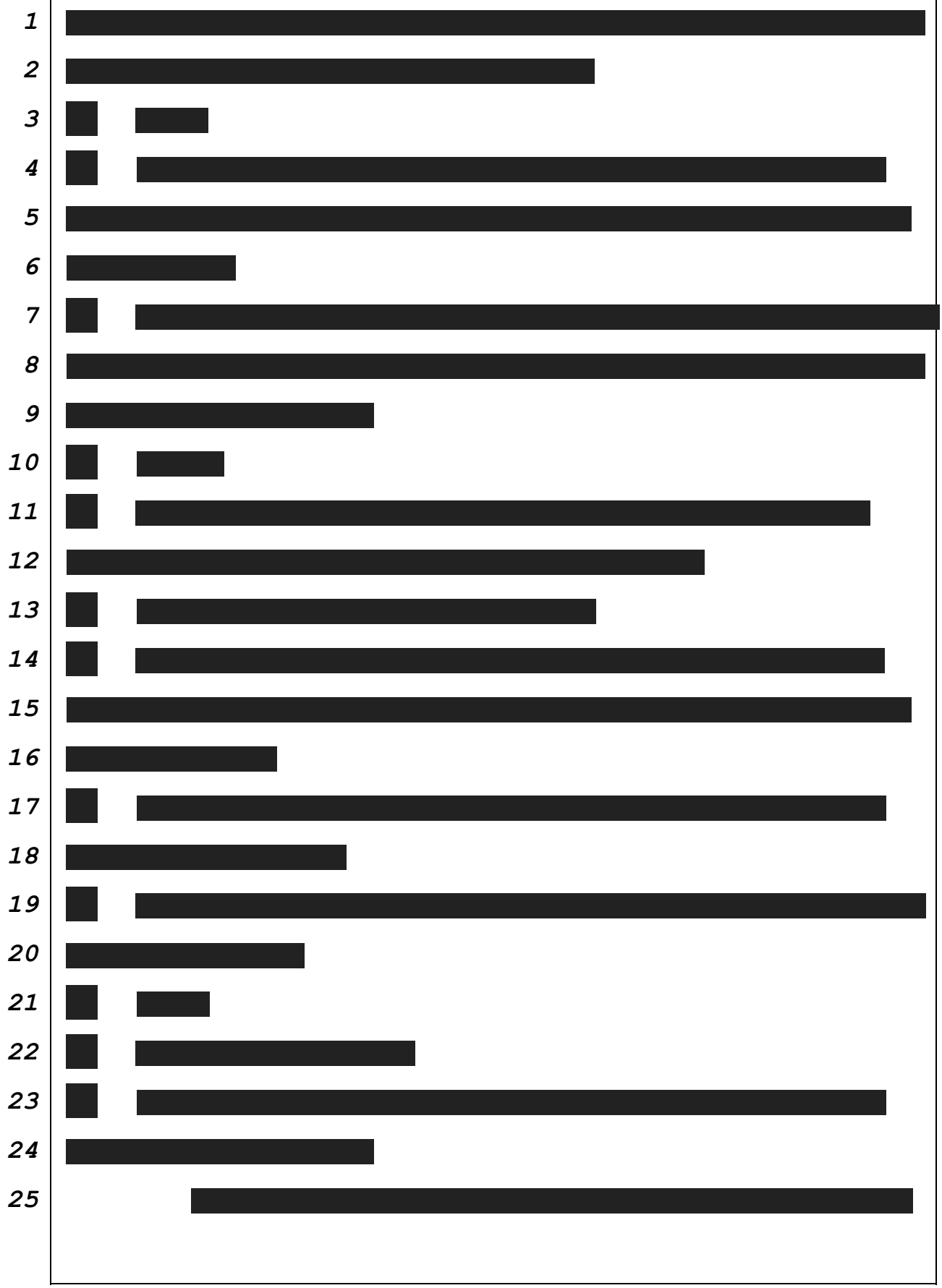


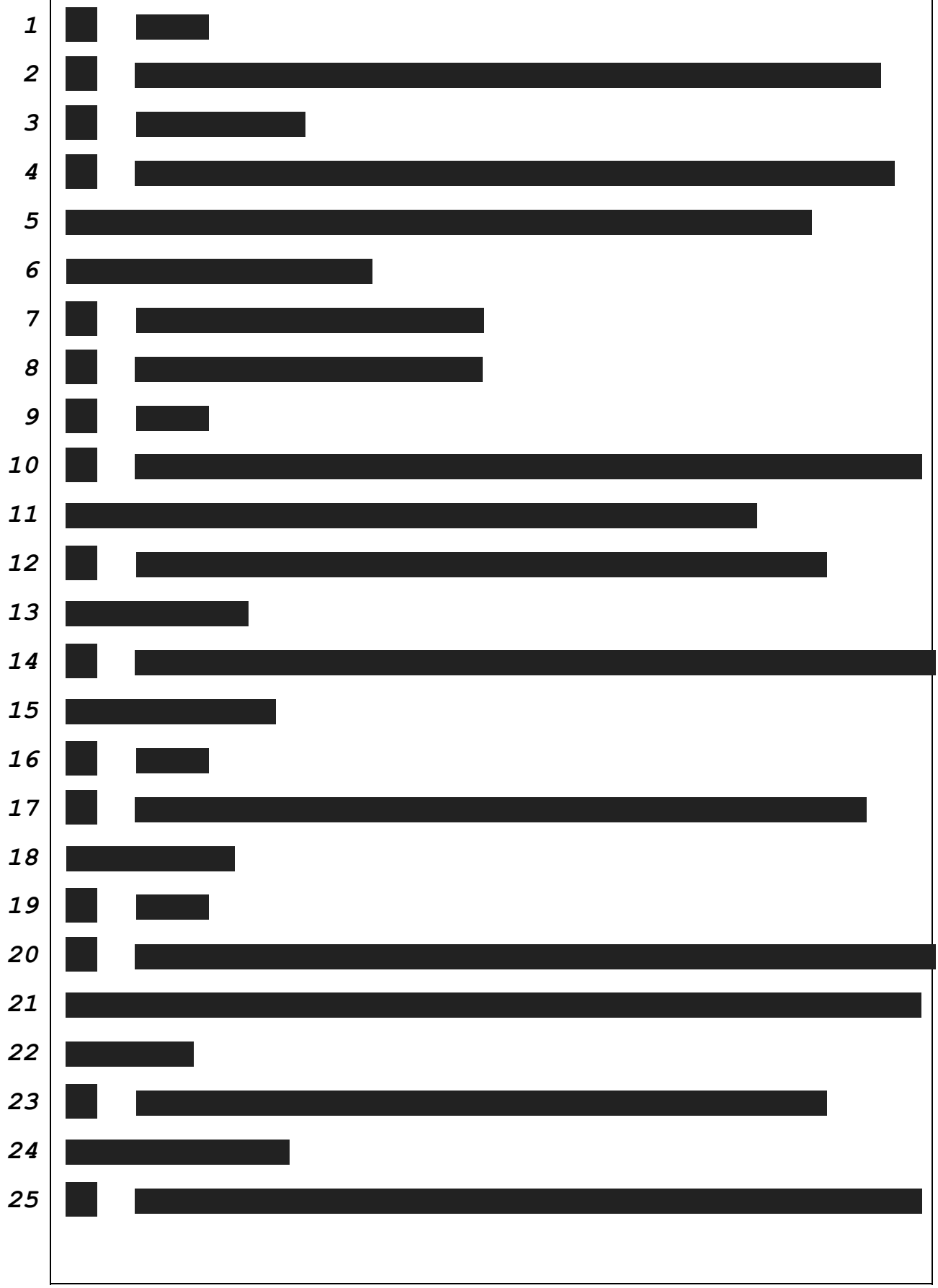


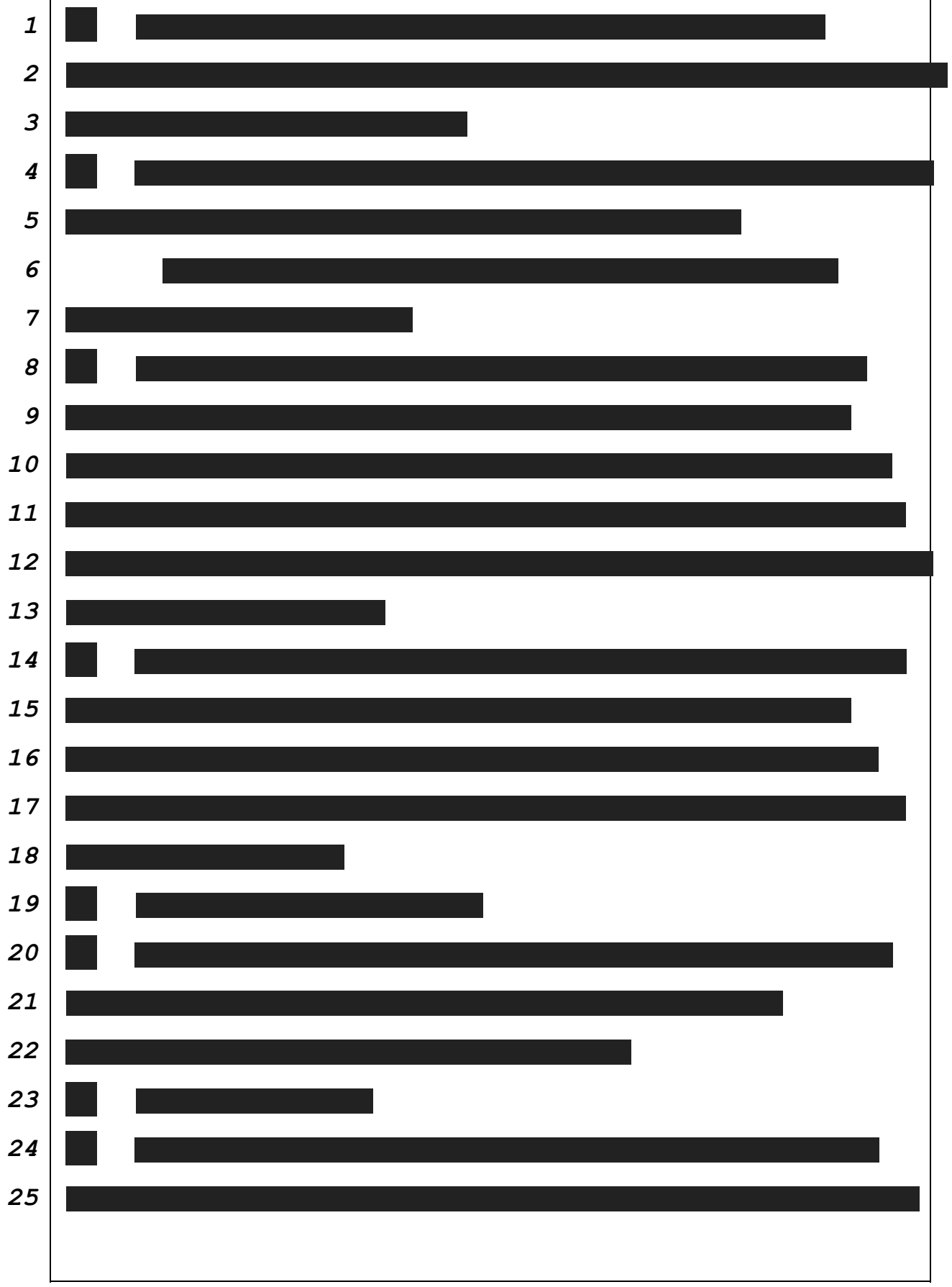


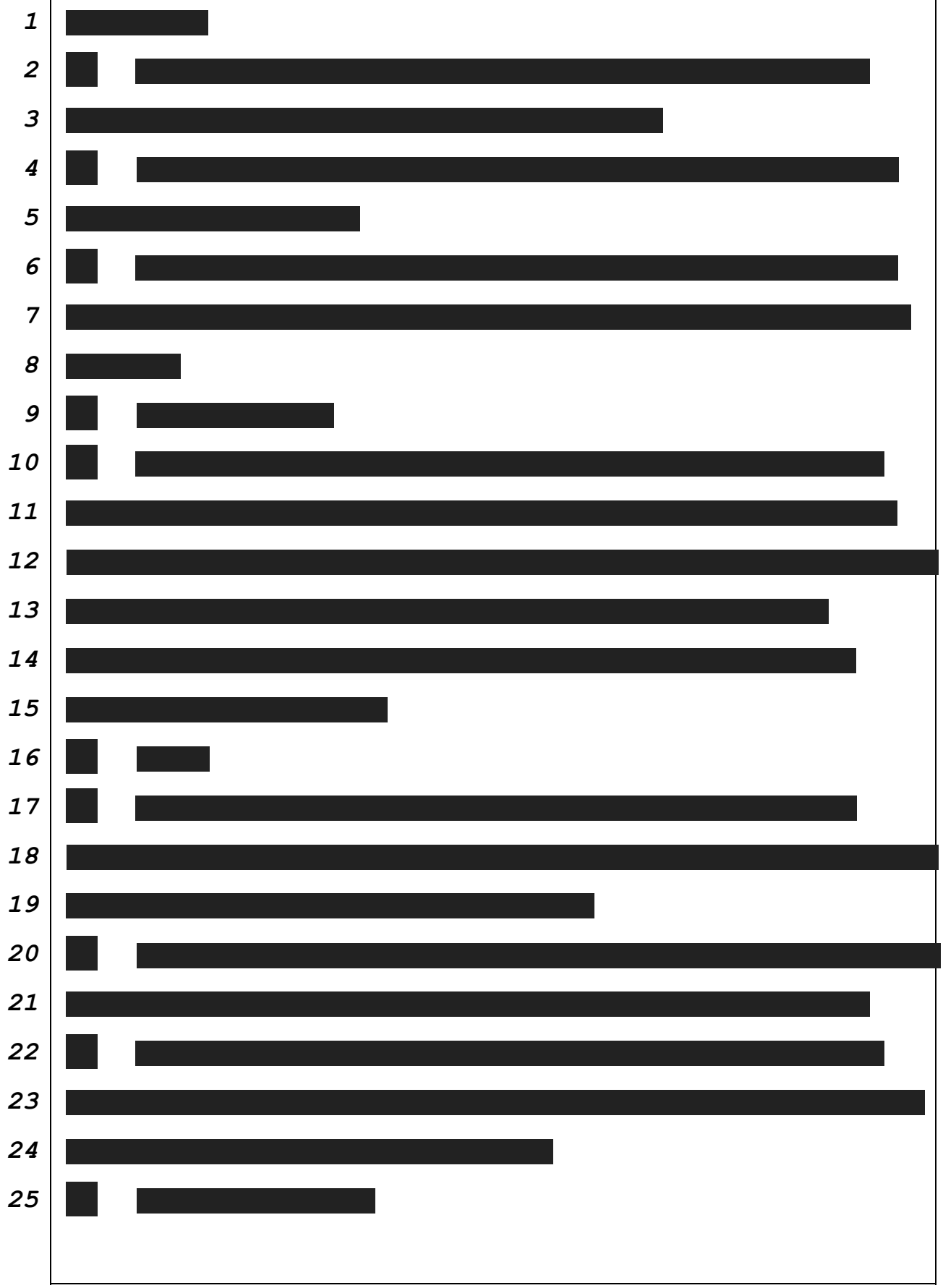


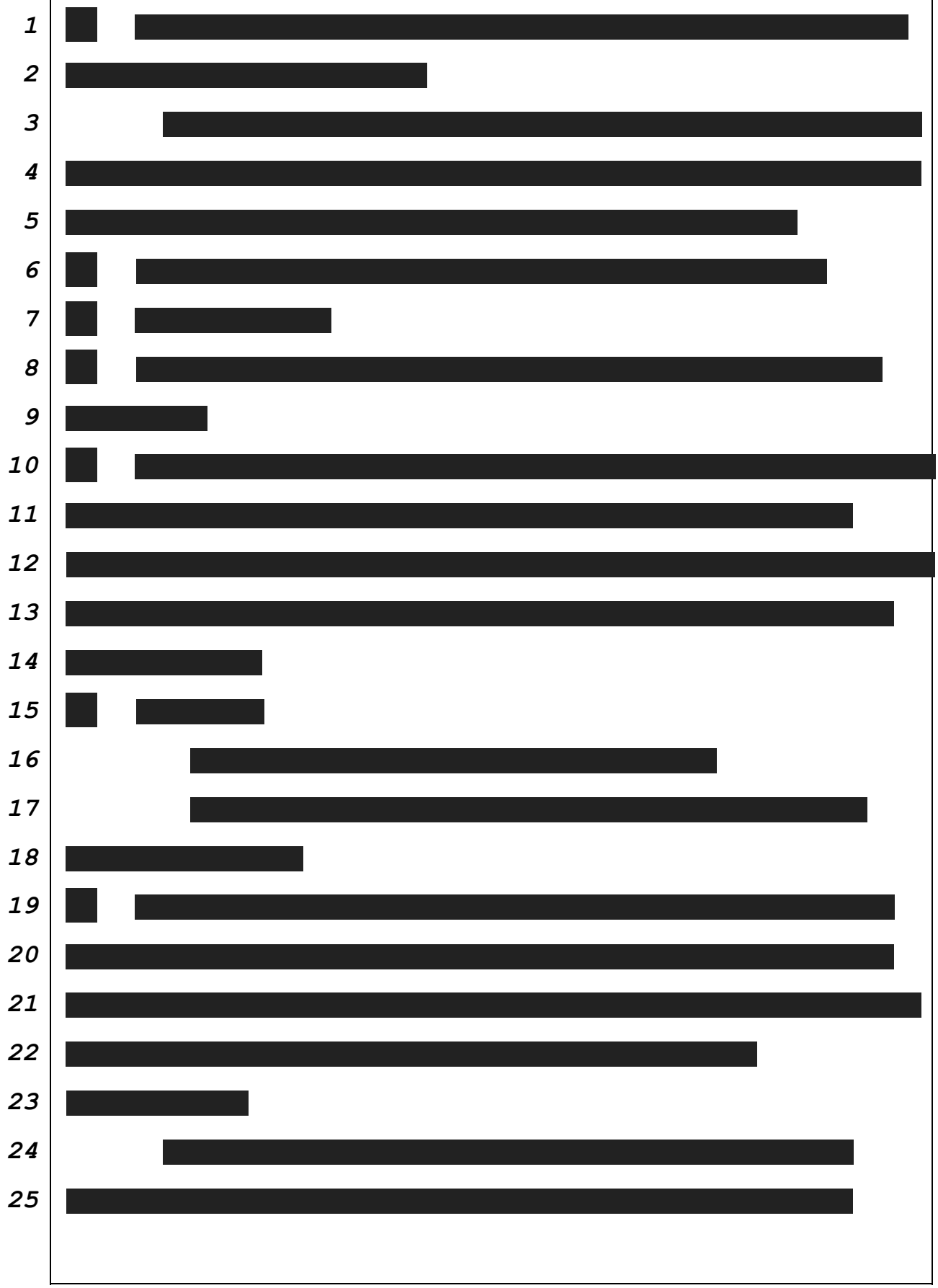


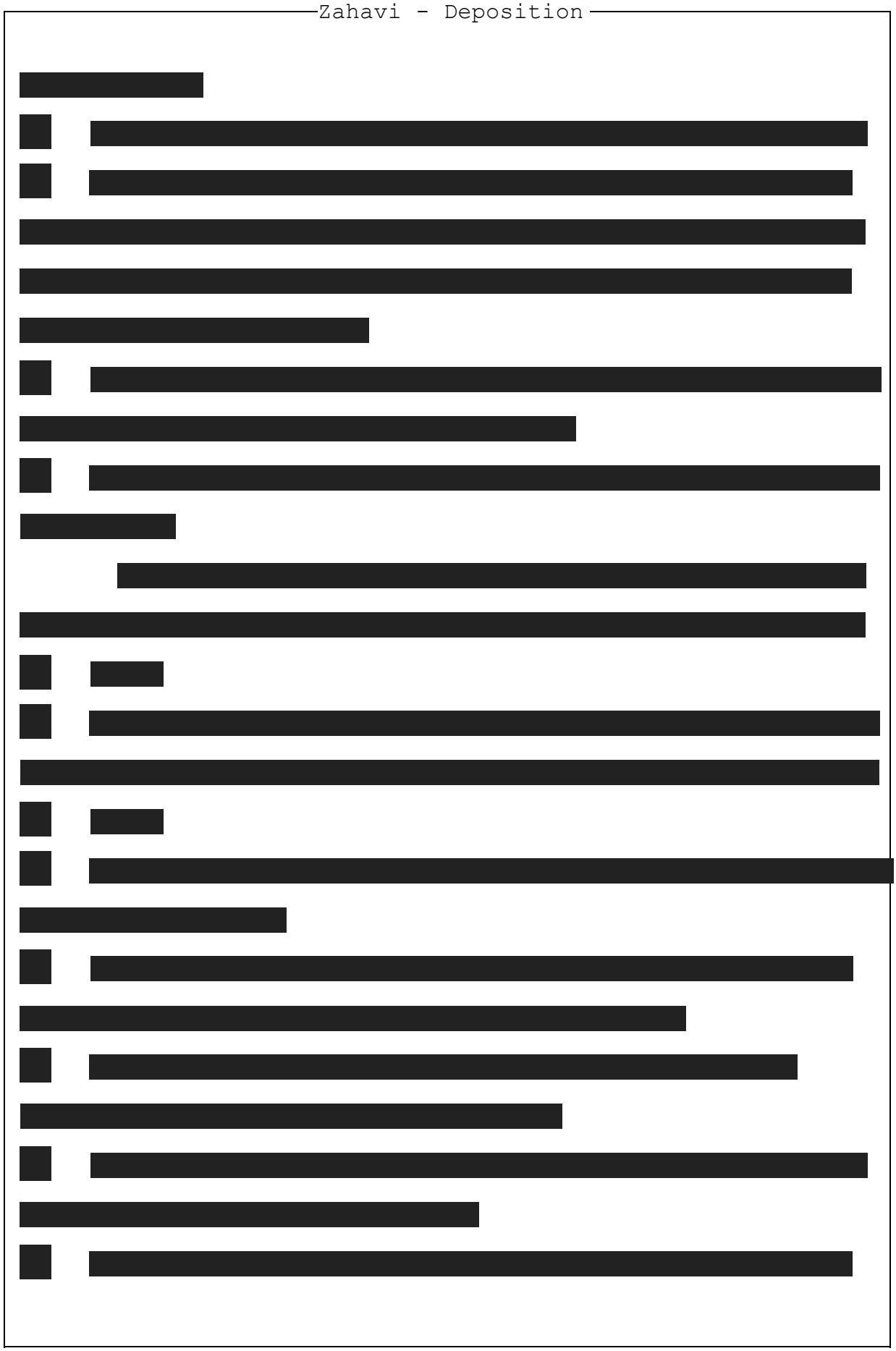


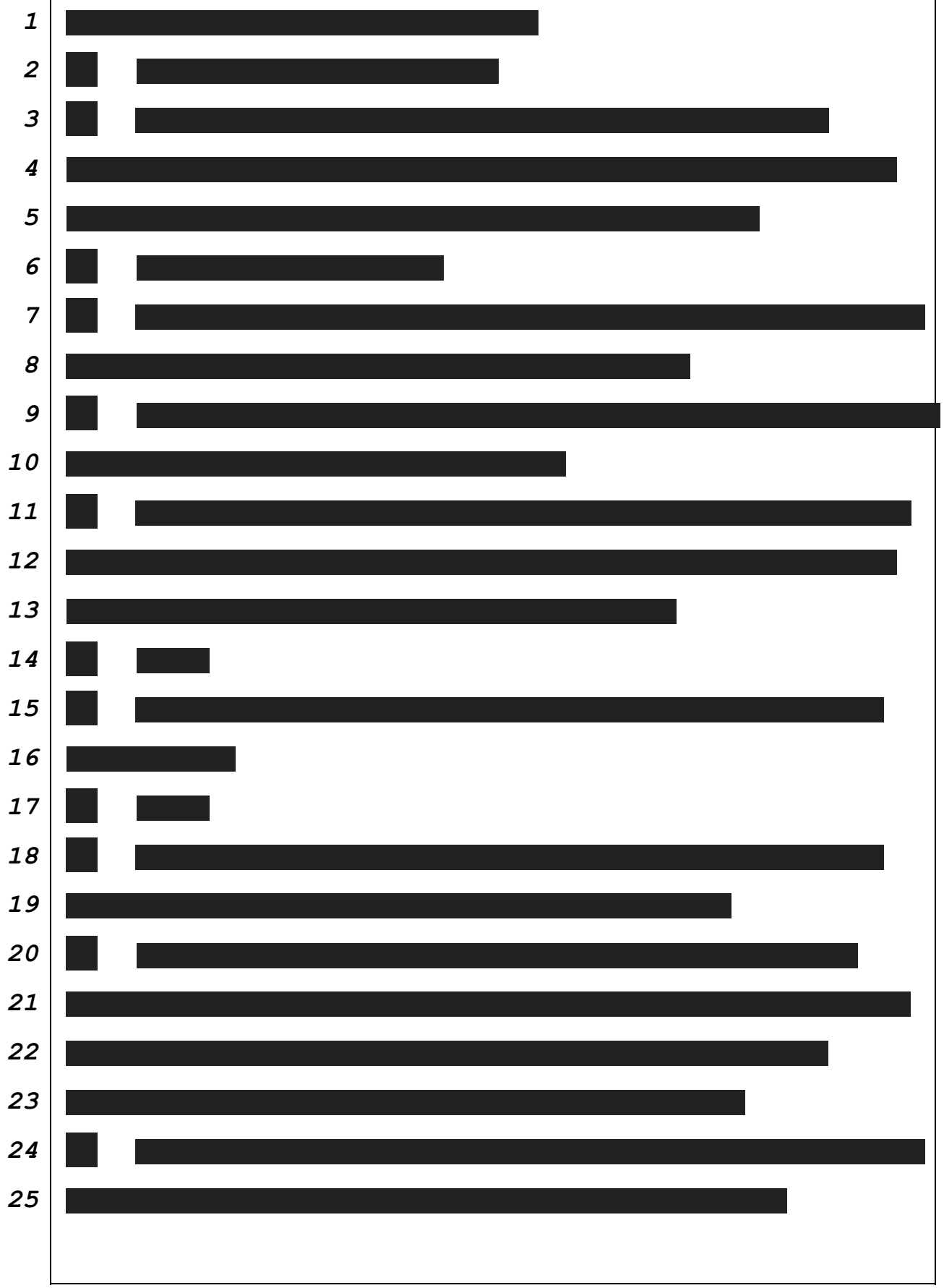


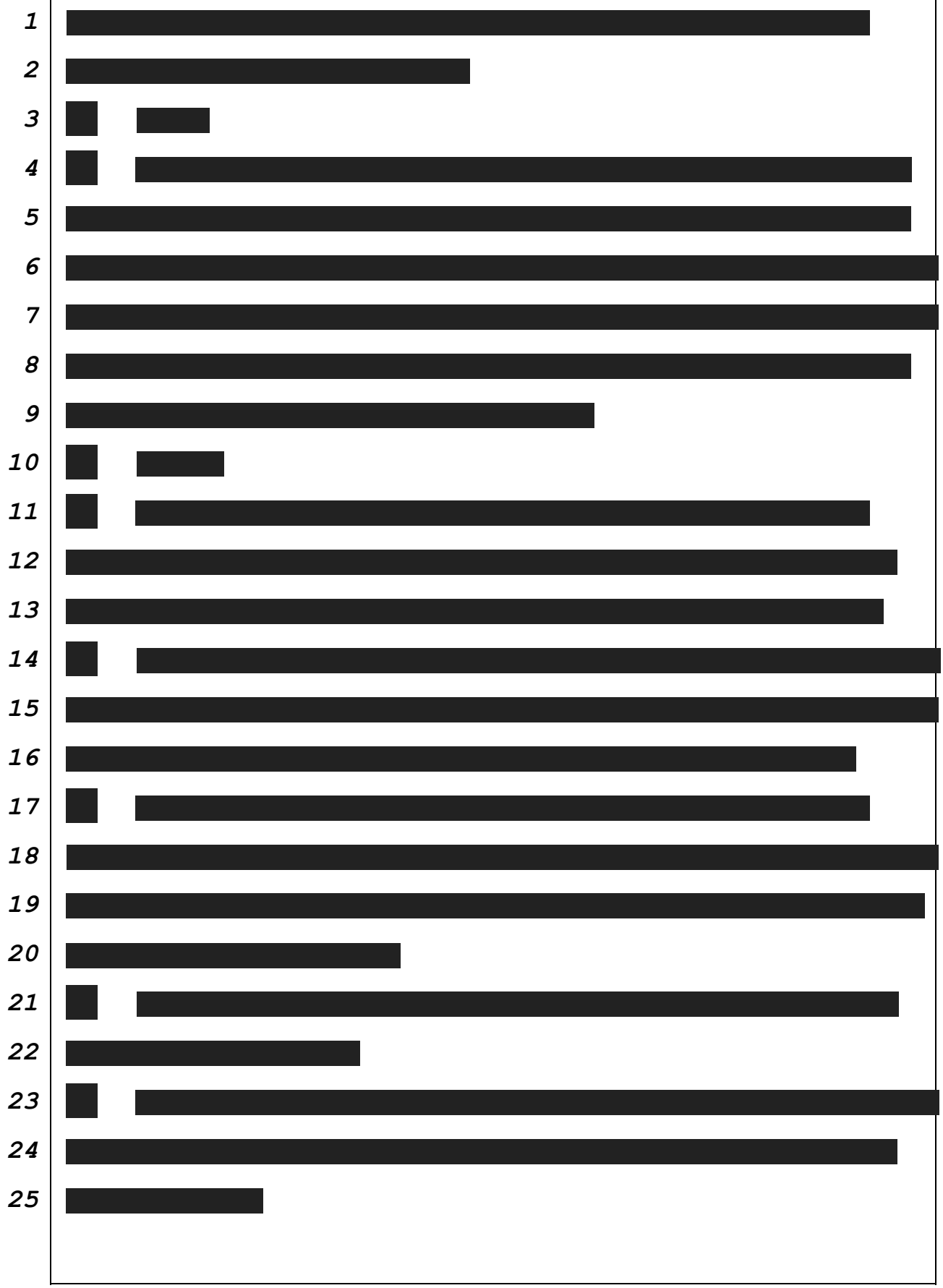












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Are you going to call the witness now?

MR. DITTMANN: Yes. I just have to grab him out of the hallway.

THE COURT: Well, look, let's take a five-minute break and then we'll start with him.

(Brief Recess.)

THE COURT: Good afternoon, Mr. Dittmann.

MR. DITTMANN: Good afternoon, your Honor. As our next witness, plaintiffs call Dr. Gordon Amidon.

(Whereupon, GORDON LOUIS AMIDON, witness for the Plaintiffs, sworn.)

THE DEPUTY CLERK: Please state and spell your full name for the record. Please have a seat.

THE WITNESS: Gordon Louis Amidon.

MR. DITTMANN: Your Honor, may I approach to hand the witness some binders of exhibits and demonstratives?

THE COURT: Of course.

VOIR DIRE EXAMINATION BY MR. DITTMANN:

Q. Good afternoon, Dr. Amidon.

A. Good afternoon.

Q. Could you please turn to PTX-78 in your binder and pull it up on the screen, please.

A. Yes.

Q. Could you tell us what this document is?

A. This is my curriculum vitae as of January of this year.

Q. And could you please summarize your educational background, starting at university.

A. Yeah, I have bachelor of science in pharmacy from the State University of New York at Buffalo, 1967. And a masters in mathematics from the University of Michigan in 1970 and a Ph.D. in pharmaceutical chemistry from the University of Michigan in 1971.

Q. What did you do after receiving your Ph.D. in pharmaceutical chemistry from the University of Michigan?

A. I joined the faculty of the University of Wisconsin.

Q. And was this in 1971?

A. In 1971, yes.
Q. And what courses generally did you teach at the University of Wisconsin?
A. Well, I taught physical chemistry, thermodynamics, chemical stability, expiration dating, experimental design, statistics, nonlinear regression pharmacokinetics.
THE COURT: Nonlinear?
THE WITNESS: Nonlinear regression analysis, a statistical method. Expiration dating, I mentioned that. Experimental design, molecular mechanics, physical chemistry courses.
BY MR. DITTMANN:
Q. Okay. Did you do any laboratory research while at the University of Wisconsin?
A. Yes, that's an extensive part of -- an extensive part of an academic career is initiating a research program, and my career, ten years at Wisconsin, I was at Wisconsin from 1971 till 1981. I established research programs in pharmacokinetics, drug metabolism, biopharmaceutics, solution physical chemistry, liquid dosage forms. Those are areas of research which I initiated and developed at the University of Wisconsin.
Q. And you mentioned solutions. Did any of your research involved I.V. parenteral dosage forms?
A. Yes, yes. And I've -- yeah.

Q. I thought I heard you say that you were at Wisconsin until 1981; is that correct?
A. Yes.
Q. And did you continue teaching after you left the University of Wisconsin?
A. Yes. For two years, I was at adjunct professor at the University of Kansas. Also my graduate program was run out of the University of Kansas. And my official -- my position was as director of research at Merck, Sharp & Dohme Research Laboratories, an INTERx division that Merck had purchased in 1980 --
THE COURT: I'm sorry, Doctor. I'm not following this too well.
You were at the University of Kansas, but your position was director of research at a company, Merck Sharp & Dohme.
THE WITNESS: I was adjunct professor at the University of Kansas.
THE COURT: Okay. And so you had a full-time position at the pharma company, and you also taught as an adjunct professor at the university?
THE WITNESS: Yes.
THE COURT: Okay. Now I understand.
BY MR. DITTMANN:
Q. And I'll come back to your time at the Merck division INTERx in a bit, but continuing your educational background,

at least teaching experience, can you tell me the types of courses that you were teaching as an adjunct professor at the University of Kansas?

A. At the University of Kansas, I taught in pharmacokinetics and biopharmaceutics in the graduate program at the University of Kansas.

Q. Where are you currently employed?

A. Well, in 1983 I moved back to academics to the University of Michigan, and I have been at the University of Michigan since 1983.

THE COURT: Your alma mater.

THE WITNESS: My alma mater, yes.

BY MR. DITTMANN:

Q. And what was your position when you first began working at the University of Michigan?

A. I was recruited back to the University of Michigan as professor of pharmacy and pharmaceutical sciences.

Q. And has your position changed while you've been at the University of Michigan?

A. Well, my -- I was promoted to the Charles Walgreen, Jr. Professor of Pharmacy and Pharmaceutical Sciences in 1994.

Q. And can you explain what this title is you have?

A. Well, it's a recognition of your contributions to the pharmaceutical sciences, your international recognition in the scientific field, your graduate teaching and training. So,

it's a level of stature achieved through your research and teaching activities.

Q. And you mentioned you were given this title in 1994. Do you still hold this today?

A. Yes.

Q. And what courses have you taught generally at the University of Michigan?

A. Again, so I've taught physical chemistry, pharmacokinetics, drug absorption, drug transport -- transport phenomena is one of my areas of research -- expiration dating, experimental design, yeah.

THE COURT: What is drug transport?

THE WITNESS: Officially called -- officially it's mass transport. Diffusion, convection, how molecules move from one part of space to the other, either as a result of a pressure gradient convection or as a diffusive gradient, which is a concentration gradient. So we refer to that as diffusion.

THE COURT: Thank you.

BY MR. DITTMANN:

Q. Besides your teaching duties, have you had other responsibilities at the University of Michigan?

A. Well, teaching and research. I mean, in an academic position today at a research university, you do both teaching and research.

And, so, yeah, you have to do both. And, so, over the course of my career, I've done extensive research with research grants with NIH and with FDA funding the graduate research program.

Q. I'd now like to turn back to your experience working at pharmaceutical companies. And you mentioned earlier that you spent some time as a director at INTERx, a division of Merck; is that right?

A. Yes.

Q. And that was in 1981?

A. Yes, 1981 to 1983.

Q. To 1983. Thank you.

What were your responsibilities as director at INTERx?

A. I was recruited by Merck to manage their drug delivery efforts, their dosage form development group at INTERx, which was a division that Merck had acquired, and I participated in managing dosage form development.

Q. Do you have any other industry experience besides your time at INTERx?

A. Yes. Well, returning to the academic sphere, which was all pull and no push going from Merck. Merck was an outstanding experience.

After joining the University of Michigan, SmithKline Beckman at the time -- it was SKB at the time, now it's GSK -- recruited me for a half-time position. And, so, for three

years I served half-time University of Michigan, half-time SmithKline Beckman directing a drug delivery effort at SmithKline Beckman.

At that time SmithKline was looking to enhance its pharmaceutical research and particularly formulation dosage form, controlled release research. And, so, they were looking to build. So my task was to build a drug delivery effort within SmithKline Beckman.

Q. And you began working as SmithKline in 1983; is that correct?

A. Late 1983, yes.

Q. Until 1986?

A. Yes.

Q. And what was your title, if you recall?

A. Again, I was director of I think pharmaceutical chemistry or, yeah, at Merck.

Q. And could you briefly describe --

A. I'm sorry, at SmithKline. Okay.

Q. Could you briefly describe your responsibilities as director at SmithKline Beacham?

A. Well, it was preformulation and formulation research. You do both within a department. They're different, usually different departments or divisions within the product development group, and you do the physical chemistry of dosage forms, physical chemistry particularly of drugs and dosage

forms, material science of a dosage form and maybe the pilot plant or clinical batch manufacturing.

Q. Did you have any involvements while at SmithKline in selecting drug molecules for development as drug products?

A. Yes. I think within both Merck and with SmithKline, the product development is always a team. There's multiple people involved, multiple considerations that require a teamwork of effort. And my experience is the manufacturing or the person involved in manufacturing are always involved with a team of scientists or skilled individuals.

Q. Have you also consulted with pharmaceutical companies in your career?

A. Yes. Over my career, I've consulted with most of the western as well as Japanese companies, many Asian countries -- companies. So I think I've probably consulted with almost every company, major pharmaceutical company, in the U.S., Europe, and Japan.

MR. DITTMANN: Can we please bring up PDX 701.

BY MR. DITTMANN:

Q. Are these some of the companies that you've consulted with in your career, Doctor?

A. Yes. I've consulted with all of these companies at different times in the past 30 years.

Q. Can you provide some examples as to the types of projects you've worked on as part of your consulting arrangements?

A. Generally, it was preformulation, formulation, and then product performance, manufacturing or biopharmaceutical performance I would say most often related to the physical chemistry or material science of the dosage form.

Q. And have you been involved in any consulting projects that involved the selection of a pharmaceutical molecule for development as a drug product?

A. I would say most of these -- many of the times there was consideration of which API and the physical chemistry of the API and matching it to a delivery system, formulation or particularly dosage form.

Q. Can you describe generally the types of scientists that worked on the selection of a molecule for development?

A. Well, the clinical, the selection of a molecule will depend on the therapeutic areas of the company it specializes in, but it would involve both clinical as well as drug discovery and development people. But particularly the clinical, the meeting the clinical need would be the principal -- I would say the initial focus. Then you define a therapeutic area, you define receptors and new chemistry, but I would say the clinical decisions are primary.

Q. Would the formulation scientist members of the team have any involvement at this stage --

A. Yes.

Q. -- of the drug development process?

A. Yes. At this stage, you have to have -- you have to develop -- you have to develop a product, a physical embodiment that you could use for your clinical application.

So I'd say there's certain, of course, physical constraints that a formulation scientist would be aware of. So, I think that the formulation scientist in terms of route of administration, what's possible, types of dosage forms would be -- would be part of that team.

Q. Now, have any of your consulting projects involved the selection of a route of administration for a particular drug product?

A. Yes. I've been involved with nasal, ophthalmic, transdermal, topical. I mean, that's route of administration is -- yeah, a common part of, you know, the product development considerations by the project team.

Q. And can you tell me what types of scientists in your experience would be involved in determining what route of administration to pursue?

A. Well, you have both clinical and the formulation scientist, sometimes the drug discovery scientist, but the principal determinants would be clinical application and clinical need and then the dosage form that could meet that need.

Q. In your experience working in and with pharmaceutical companies, how many different routes of administration are

typically focused on at any one time?
A. Well, in terms of the product development effort for a particular -- for one compound, I would say, you focus on what you think is your best chance, best opportunity for clinical efficacy and clinical -- meeting a clinical need. So, I would say a POSA, a product development person, would focus on one product at a time.
Q. And by one product, do you mean one dosage form at a time?
A. One dosage form, yeah, yeah.
Q. And why is that, Doctor?
A. Well, because of the extensive requirements that you need to meet in order to get an approved dosage form and approved -- and approved indication. And there's generally -- not a lot of time, so you want to move the product along quickly.
So I think the time pressures and the number of studies that you need to do, a POSA can only do one project at a time. Now, a given company might have multiple people, you know, multiple teams, multiple departments, but a given team would be focusing on one product.
Q. Have you formed any companies in your career?
A. Yes, I have. Yes, I've formed -- following my experience at SmithKline, which was a lot of effort, I decided to go back to academics where I could do more, promote more of the type

of research I felt was needed in the pharmaceutical sciences.

THE COURT: So, that was full-time academics.

THE WITNESS: Yes, back full-time, correct. Full-time academic, 1986 I went back full-time to the University of Michigan and in 1986 I formed a drug delivery company, TSRL, Inc., where we could continue doing product-related research in the usual product environment, which requires confidentiality and, generally, some time frame for completing the project, which is not easy to do in an academic program with graduate students and graduate student research, so I formed a company to do contract work -- that could do contract work based on the expertise of the people in the company, while keeping my academic graduate research program separate.

BY MR. DITTMANN:

Q. Is TSRL still an active company today?

A. Yes, it continues. It's still -- it's been in continuous operation since 1986.

Q. And would it be accurate to refer to TSRL as a contract research organization, or CRO?

A. Yes.

Q. Now, aside from TSRL and the consulting work we just discussed do you have any other educational experience in the pharmaceutical field?

A. Well, in addition to my teaching at the University of

Michigan, we have taught biopharmaceutics courses and drug delivery courses alternating U.S.-Europe since about 1984 and 1985.

We continue to teach those courses, and, as I say, alternating every year U.S., Europe, teaching mostly industrial scientists, you know, drug delivery and biopharmaceutics. Some regulatory scientists. We also do workshops at the FDA and continue to do workshops at the FDA on product development, product regulatory science.

Q. Now, is the teaching you just mentioned, is this done through a particular organization?

A. Well, I have a not-for-profit -- well, initially, it was done through the University of Michigan, but the international courses have been managed by not-for-profit company called The Drug Delivery Foundation.

Q. You mentioned earlier that you've taught some courses at the FDA. Have you ever worked with the FDA or worked at the FDA, I should say?

A. Yes. I've worked with the FDA since early in my career at Wisconsin, doing pharmacokinetic research for the FDA. But I actually worked at the FDA. I took a one-year sabbatical in 1990 and spent one year at the FDA, working with the FDA scientists in the biopharmaceutics department or group within FDA.

Q. And was your --

THE COURT: Just a second. When a professor goes to the FDA for a tour of duty, is that person an FDA employee, appointee of some sort?

THE WITNESS: I was appointed as a visiting scientist, and I was paid through a grant to the University of Michigan, so I still was -- I was on sabbatical, official sabbatical from the University of Michigan. And on sabbatical from Michigan, you get half salary for a year, and then the FDA paid the other half of my salary through a grant to the University of Michigan.

THE COURT: That makes sense.

BY MR. DITTMANN:

Q. Was your one-year sabbatical at the FDA the result of an invitation from the FDA?

A. Yes. I think the FDA was undergoing a transition at the time. You know, the FDA really expanded dramatically after the 1962 laws, regulations. The FDA really expanded enormously in the sixties, and by the nineties scientists had evolved. And, so, the FDA wanted to increase and improve its standards and at the time, I think there was a big reinventing government or whatever by the Clinton administration.

So the FDA wanted to improve its regulatory standards and reduce regulatory burden. So, at any rate, so I was recruited in to assist in the development of the FDA's biopharmaceutical standards.

And as a result of that -- and I've worked continuously with the FDA since then, developing actually -- ultimately, in 2000 a guidance was published, an FDA regulatory guidance was published based on the research that I had done with the FDA over the 1990s, which was initiated after my sabbatical at the FDA.

So, I've worked extensively, continue to work with the FDA as a consultant. I've served on pharmaceutical sciences advisory panel, originally the generic drug advisory panel. Now it's the pharmaceutical sciences advisory panel, and I have presented to that panel as a consultant.

So, I've been a big promoter of regulatory science standards in the field and academic involvement in regulatory science standards, sure.

Q. Thank you for that, Doctor. I'd like to turn next to your publications.

Can you tell us roughly how many articles you have published over the course of your career?

A. Well, as my graduate research program, I would say I published more than 350 peer-reviewed papers and, I don't know, maybe 30 monograph chapters in regulatory science.

Q. And, have you --

A. I'm sorry, science, including regulatory science.

Q. Have you authored any books?

A. Yes, I've authored monographs, as well as been the

principal editor of several books, including a book on transport phenomenon pharmaceutical systems, and then probably more well known for a book on chemical stability of pharmaceuticals.

MR. DITTMANN: May I approach the witness, your Honor?

THE COURT: Sure.

BY MR. DITTMANN:

Q. I'm now handing you, Doctor, what's been marked for identification as PDX 726. Do you recognize this as the book you just mentioned, The Chemical Stability of Pharmaceuticals?

A. Yes. This is the second edition of the book on The Chemical Stability of Pharmaceuticals published with my co-authors Professor Kenneth Connors of the University of Wisconsin and Professor Valentino Stella from the University of Kansas. The second edition was published in 1986.

Q. And do you know whether today your book is still being used by pharmaceutical scientists?

A. Yes. I think it's still a common reference book because it pretty much summarized the field of chemical stability and expiration dating through the sixties, seventies and into the eighties when the science of expiration dating, you know, the process, the data that you need to generate to stick your expiration date on your pharmaceutical product.

That science was developed in the '60s, '70s and '80s,

and it pretty much summarized that level of science, and it still is a principal reference book, I think.

Q. Are you also involved with any pharmaceutical journals?

A. Yes. Over the course of my career, I've been an associate editor and on the editorial board for JPharm Sci, Journal of Pharmaceutical Sciences, Pharmaceutical Research, and International Journal of Pharmaceutical Research. And I'm currently the editor-in-chief for the American Chemical Society Journal, Molecular Pharmaceutics.

Q. And have you received any awards in your career?

A. Yes. Over the course of my career, I've been able to achieve the Best Paper Award in the '70s and '80s and '90s even in JPharm Sci and Pharmaceutical Research.

I have received the highest research achievement awards from the Controlled Release Society, as well as the American Association of Pharmaceutical Sciences. I've received the honorary degree from two universities, the University of Uppsala in Sweden and Miguel Hernandez University in Spain.

I've received the highest award from the American Association of Colleges of Pharmacies for teaching and contributions to pharmaceutical sciences, so I've been -- been fortunate to receive a fair amount of recognition, yeah.

Q. And have any of your awards, Doctor, related to your work in the field of parenteral formulations?

A. Yes. In fact, I have received an award from the Journal

of the Parenteral Drug Association, yes.

MR. DITTMANN: At this time, plaintiffs offer Dr. Amidon as an expert in the field of pharmaceutical product development and formulation design.

MR. LOMBARDI: No objection, your Honor.

THE COURT: Yes. And thank you for your patience in listing all of your --

THE WITNESS: No, thank you.

THE COURT: -- and summarizing all of your career achievements.

DIRECT EXAMINATION BY MR. DITTMANN:

Q. Dr. Amidon, can you tell us what you were asked to do in connection with this litigation?

A. Yes. I was asked to consider the science, the scientific basis for the patents-in-suit and, also, to consider the assertions of the plaintiffs in this case regarding the validity of the claims in the patent-in-suit.

Q. You're referring to the defendants' claims?

A. I'm sorry. I'm sorry. I get defendants and plaintiffs mixed up.

Q. Okay. Have you prepared a set of slides setting forth your opinions in this case?

A. Yes, I have.

MR. DITTMANN: Can we please bring up PDX 702.

BY THE WITNESS:

A. Yes. So, here it summarizes very briefly, and I'll use a laser pointer at times, but a POSA, which is an abbreviation for person of skill in the art, had no motivation to add a chelating agent such as EDTA to the formulation.

And then there's additional objective indicators or indicia I understand of nonobviousness, including the long-felt need in the area of emesis, the commercial success, ultimate commercial success and recognition, and then the unexpected properties of the formulation.

BY MR. DITTMANN:

Q. And your opinions in this case relate to four patents, correct, Doctor?

A. Yes.

MR. DITTMANN: Can you please bring up PDX 703.

BY THE WITNESS:

A. Yes. So, the four patents are listed here, and the field of invention is antiemetic drug products.

MR. DITTMANN: And can we please bring up DTX-69.

BY MR. DITTMANN:

Q. It's the first patent we saw mentioned there, the '724 patent?

A. Yes.

Q. And you've considered this patent in your analysis, correct, Doctor?

A. Yes.

MR. DITTMANN: Can we please go down to the bottom right of the first page, focusing on the abstract.

BY MR. DITTMANN:

Q. And I'll just read into the record, the first sentence states, "The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy-induced emesis with palonosetron."

Do you see that, Doctor?

A. Yes.

Q. And what is this referring to?

A. Well, I would pick out the shelf-stable liquid formulation of palonosetron. That's a key indicator. You want a shelf-stable something that you can commercialize and store, ship and administer for reducing chemotherapy and radiotherapy-induced emesis.

So, that's -- that's the key objective of the -- of the technology patent in this patent.

MR. DITTMANN: I would like to look next at the claims you've considered. Can we bring up PDX 704.

BY MR. DITTMANN:

Q. And do you consider this claim we have on the screen here, Claim 9 of the '724 patent, to be representative of the claims of the '724, '725 and '424 patents you've considered?

A. Yes, yes, and I've highlighted a key component here is including a chelating agent, which I will discuss more in this

direct testimony, but that's -- this is the key -- key claim.
Q. This is the portion you'll be focusing on --
A. Yes.
Q. -- in your discussions?
A. Yes.
MR. DITTMANN: Please bring up PDX 705.
BY MR. DITTMANN:
Q. And it sets forth Claim 1 of the '219 patent. Can you explain what portions of this claim you will be focusing on in connection with your opinions today?
A. Well, again, this is focused on cancer chemotherapy and method of treatment. But key here I'm focusing on the EDTA and the inclusion of EDTA in this formulation.
Q. Before we go into the details of your opinions, do you have a slide summarizing the legal standards that you applied in reaching your conclusions?
A. Yes. I've summarized those. I mean, I'm not an attorney, but I understand from counsel here the legal standards that are applied, and I think I have those in a transparency or slide.
MR. DITTMANN: Can we bring up PDX 706.
BY THE WITNESS:
A. Yes. So, here's, you know, I've been asked to consider the patents and whether the differences between the claimed subject matter and the prior art are such that the subject

matter as a whole would have been obvious to a person skilled in the art. And, so, this is the broad objective that I've been given.

And in considering this is considering the scope and content of the prior art as of the date 2002, 2003 as presented to me, the prior art from that time, versus -- and then the differences between the prior art and the claims at issue. Also, the level of skill of a person skilled in the art in the field of invention at this time.

And then finally these obvious indicators or objective, I'm sorry, indicators of nonobviousness. So, those are the components of my -- the legal standard, as I understand it.

Q. And we see here on the slide mentioning a POSA or a person of ordinary skill in the art. Did you define the person of ordinary skill in the art for purposes of your analysis?

A. Yes, I did. I've worked with, trained, directed many POSA, I mean, even today at my company TSRL, so based on my experience, I have a definition of a POSA.

MR. DITTMANN: Let's take look at that. Can we bring up PDX 707.

BY MR. DITTMANN:

Q. And can you explain what we're seeing here, Doctor?

A. Yes. So here a person of ordinary skill in the art I would take as a person actively involved in the development of

pharmaceutical products, of course. And it involves a number of disciplines. It's really a project team that requires a collaborative team of people involved in decision making.

The degree in chemistry typically or pharmaceutical chemistry particularly, sometimes pharmacy or medicine or clinical pharmacology and general pharmaceutical science, chemistry-related field, generally with a relevant experience of two, three, four years, depending on the level of education, and the person would have either a B.S., M.S. in the scientific area or Ph.D. or M.D.

That would be a typical person as part of this -- the typical collection of people that would be part of this POSA expertise.

THE COURT: Somebody would have to know something about statistics or not?

THE WITNESS: There generally are statistical departments. I would say most pharmaceutical scientists know, biological scientists know something about statistics and statistical computations.

I would say the ultimate statistics that you get into with clinical design and evaluation of clinical efficacy, such as the FDA would do, can be quite complex, but normal statistics with regard to experimental data, that would be a common part of training.

BY MR. DITTMANN:

Q. What information and documents did you consider in forming your POSA definition?

A. Well, in addition to my own experience, of course, I looked at the patents-in-suit and looked at the intent there and the skills that I thought would be necessary for the patents-in-suit, but -- yeah.

MR. DITTMANN: Could we bring back up PDX 701.

BY MR. DITTMANN:

Q. And I think you alluded to this, Doctor, earlier, but is it correct that these companies that you've consulted with over your career, did they employ in your experience individuals meeting the qualifications of a POSA you've set forth?

A. Yes. Yes. I've interacted with many teams of formulation and product development scientists at these companies over the years, so, yeah.

THE COURT: Would one individual possess the array of knowledge, training, and experience to qualify as the hypothetical POSA?

THE WITNESS: I think a POSA, a person skilled in the art, would be aware that you would need multiple pieces of information for your product design and clinical efficacy and would call on other persons as part of your team to make decisions.

And, so, would one person encompass all of the

knowledge? No. I think you would have to pull in, and my experience is project teams are always part of the product -- always part of the product development process. But a POSA would be well aware that multiple pieces of expertise are required to make the decision about product development and formulation and dosage form.

THE COURT: And I suppose the team leader would have a concept of what each discipline can contribute as they go along --

THE WITNESS: Yes, very --

THE COURT: -- know who to ask what.

THE WITNESS: Very much so. Yes. That's essential. Yes.

MR. DITTMANN: Can we please bring up DTX-0268.

BY MR. DITTMANN:

Q. And do you recognize this document, Doctor?

A. Yes. This is one of the patents I've considered, the '219 patent, yes.

Q. If we can look at the inventors on this patent, do we see towards the bottom of the list Kathleen M. Lee?

A. Well, I note I mean, Kathleen Lee is a POSA. She's actually one of my former graduate students. She worked at Syntex prior to coming back to graduate school, and then came back and worked with me as a graduate student getting her Ph.D. degree I think in the middle '90s and then went back to

Syntex and actually worked on this product.
Q. And, so, you mentioned that Kathleen Lee met the qualifications of a POSA. Was that when you began training her?
MR. LOMBARDI: Your Honor, I object. There's -- the doctor is here as an expert, not as a fact witness, and I don't believe we've had any notice that he had any particular relationship with this individual or was going to vouch for her qualifications as a POSA.
THE COURT: With that objection in mind, I'll allow this just as illustrative, but I won't give it much weight.
MR. LOMBARDI: Thank you, your Honor.
BY MR. DITTMANN:
Q. So, Doctor, Kathleen Lee in your view was someone who met the qualifications of your POSA when you began training her; is that correct?
A. Yes.
Q. Now, do you understand that Dr. Kirsch, one of defendants' experts in this case, has offered his own definition of a POSA?
A. Yes, I do.
MR. DITTMANN: Can we please bring up PDX 708.
BY MR. DITTMANN:
Q. Can you tell us does Dr. Kirsch's definition differ from yours?

A. Yes. Dr. Kirsch's definition differs from mine in that it's much more restrictive, I think. As I interpret what he said, I think this is in his direct testimony, and, in particular, Dr. Kirsch focused on a formulation scientist, but he said that even in the absence of a project team, which in my experience a POSA is always working -- always working with a project team, a POSA would draw on the knowledge and expertise of clinicians. That's essential.

So, I think the key difference here as a POSA is not just a formulator, but encompasses an interdisciplinary team, drug development team. That's my experience. That's the way I would say it always works in the pharmaceutical industry.

Q. Thank you, Doctor.

Now, before turning to the substance of your opinions, I want to briefly discuss the process of developing drug products.

MR. DITTMANN: Can we bring up PDX 709?

BY MR. DITTMANN:

Q. And is this a demonstrative that you had prepared, Doctor?

A. Yes. This probably describes the process of drug product development where you will select a candidate drug molecule in a therapeutic area that tends to be the focus of your company in one, two, three sometimes more pharmaceutical areas.

So you select a candidate drug and have a drug

discovery effort usually focused on a receptor, particular receptor. And then you'll select a candidate. At some point, the project team will select a candidate to move into drug development, where you go into drug metabolism, formulation, development, preformulation development, I should say, and at that point you look at the route of administration and dosage form.

And then the third step is considering your dose and volume, the clinical parameters for your potential product that you're developing. And then ultimately your stability and manufacturability issues are considered.

So, a project team would consider all of these, and a POSA would be involved in all of these steps in the drug development process.

MR. DITTMANN: Can we bring up next to this Kirsch Demonstrative 6.

BY MR. DITTMANN:

Q. And do you recognize, Dr. Amidon, this demonstrative that Dr. Kirsch referred to during his testimony in this case?

A. Yes. I'm familiar with this. I mean, I think as I understand Dr. Kirsch's presentation, he focused on this product profile, which kind of comes down from heaven, I guess. And then, you know, there's the physical chemistry and preformulation science and product development.

So, I think the first two or three steps here that I

think of as part of a project team were incorporated into this product profile, and the formulation scientist in Dr. Kirsch's definition would focus just on this part, which I don't agree with. I think --

THE COURT: Which part?

THE WITNESS: The preformulation and product design part. This is what a formulator -- is required of a formulator to work with the actual formulation of the product. But the product the formulator would be involved in all of these steps because, you know, you have a drug molecule, but you have to put it in a dosage form, route of administration, and then it has to be manufacturable.

So, my view of a POSA would be a POSA would be involved with all of the steps. So, I viewed Dr. Kirsch's definition as more limited than in my experience.

BY MR. DITTMANN:

Q. And by all of the steps, Doctor, you're referring to all the steps set forth in both your demonstrative we see on the screen as well as Kirsch Demonstrative 6?

A. Yes. Yes.

MR. DITTMANN: Can we focus back --

THE COURT: Let me just see if I understand your answer.

Doctor, are you talking about what the drug formulator's involvement would be in the overall stages of

progression to come out with a proposed drug --

THE WITNESS: Product.

THE COURT: -- product; or are you talking about the process itself?

In other words, if you've got a formulator, is that formulator involved in the whole process; and, if so, what, in your view, is the whole process? You've put up on the board a process.

THE WITNESS: Yes.

THE COURT: But you're talking about a formulator as you're testifying.

THE WITNESS: Well, as one of the individuals in the process, and the formulator is involved and the formulation scientist in the whole process.

So I view that as a project team and that the formulator is a component of that and a key component. I mean, there's several key components, but the process is an integrated process.

I mean, a formulator doesn't work in a vacuum. You work with the knowledge from other fields and expertise, and I think even Dr. Kirsch's definition said that the POSA would consult with a clinical person, which you would have to.

THE COURT: Okay. So, you have a four-step process, and he has a three-step process with a blue input --

THE WITNESS: Product, yeah.

THE COURT: -- item, which would be --

THE WITNESS: Product specification, yeah.

THE COURT: And, so, although you use different words, your slides, in terms of process definition, are not that different, are they? How are they different?

THE WITNESS: No. I mean, I think the difference is that the product profile in Dr. Kirsch's definition is something that might -- like, you get a report and the formulator is charged, okay, this is what we want to do; you go make it. My position is the formulator is involved in the product profile.

THE COURT: Okay. I thought I understood that to be your point.

BY MR. DITTMANN:

Q. And just if we can focus just on PDX 709 for one moment. Just to make sure the record is clear, it's your experience that the formulator team member of this development team would be involved with all four steps seen on PDX 709, correct?

A. Yes.

Q. Now, we have talked about the first two steps a bit already in connection with your background.

With respect to this third step we see here, considering the dose, volume, clinical parameters, can you briefly describe how this work is typically accomplished in a drug development team?

A. Yes. I mean, I think that this comes from the clinical parameters, the dose, the efficacy of the drug -- of the drug and, so, you have to provide a dose that would be effective, and you have in this case for a parenteral product, use a volume that could be administered. So, those parameters come from the clinical considerations for the product.

Q. Once the dose -- we'll start with that, once the dose or doses to be pursued are selected, are the formulation team members able to consider the use of doses outside the range selected?

A. No. No. You focus on what you need.

Q. Moving next to volume, once the volume has been selected by the development team, do the formulation team members have any flexibility with respect to the volumes that they suggest for development as a product?

A. A very small branch of volumes. I mean, it depends on the product, but in a case of an injectable product you would have a range of 1 or 2 mL maybe 5 mL, but you have a very small range of volume, so I would say there's a small amount of adjustability for the volume of your product, but no adjustment regarding dose.

THE COURT: In this particular project, if you were changing it to a different dose you would be having to start off a different project, right? Is that what you're saying?

THE WITNESS: Yeah, well, the particular API, the

particular drug that you're working on would have a projected dose, and, so, you would be working with your formulation and preformulation parameters in that dose range. And, yeah, the science -- as a scientist I would say I'm interested in what happens in other ranges, but a development scientist would focus on the ranges that he needed to make into a product.

Q. And, so, you would be focusing on the ranges that came from the clinical considerations, correct?

A. Yes, yes, yes, correct.

Q. Now, I want to turn to the fourth step in the process considering stability and manufacturability issues. Can you first describe why stability is important for a pharmaceutical product?

A. Well, in my experience I mean, of course, you have to make a commercial product. You have to manufacture it, store it, transport it, get it to the site, administer it to the patient. I would say the pharmaceutical companies that I have worked with have always used a two-year shelf life as a minimum standard. You needed a two-year shelf life in order to be able to commercialize a pharmaceutical product and that was the standard. I mean, of course, if it is longer that's great. I would say the time frame of the companies I worked with you want a shelf life between 2 and 5 years.

THE COURT: Some of these things can't be maintained at room temperature, they have to be refrigerated for mass

distribution, right?

THE WITNESS: That's correct. And that makes it more difficult because you have to have cold storage and a cold chain, and, so, that's a less desirable -- I mean, if there's no other way to stabilize a product, other than refrigeration or maybe freeze drying and shipping a product that would be reconstituted at the site, which is what we do with antibiotics, for example, yeah, but cold storage would be would be one method of handling a stability issue, but not the preferred method.

BY MR. DITTMANN:

Q. Now, do all pharmaceutical molecules have stability issues?

A. No.

Q. It varies from molecule to molecule?

A. No. It varies from molecule to molecule. It is very much -- very drug chemical dependent.

Q. Can we bring up DTX-0271. And do you recognize this, Doctor, as a Pharmaceutical Preformulation and Formulation Practical Guide?

A. Yes. We have a number of texts from the eighties and nineties until today on Pharmaceutical Preformulation and Formulation Guidelines that a normal POSA would -- would be well versed in, yes.

Q. And can we please turn to the second page. And what do

we see here, Doctor?
A. Well, this is a particular article, a particular chapter in that book on parenteral dosage forms by a scientist from AstraZenica.
Q. And is this the Broadhead 2001 reference that Dr. Kirsch discussed during his testimony in this case?
A. Yes.
Q. Would you please turn to Page 5.
I want to focus at the bottom under the "Choice of Excipients" heading. And I'll read into the record the first sentence. "As with all pharmaceutical products, the most important rule to bear in mind when formulating parenterals is the 'keep it simple' principle."
Do you see that, Doctor?
A. Yes.
Q. Can you explain what this principle means?
A. Well, this is kind of the golden rule the formulation -- for all pharmaceuticals, especially true for parenteral products is you only include in the formulation what you need and what you can justify based on some need. So, you do not add anything you don't need to the product. So, this is kind of a golden rule for formulators.
Q. Can you explain how this "keep it simple" rule for I.V. formulations would apply in the situation you mentioned earlier where there did not appear to be a stability issue?

A. Well, as I think we will discuss during my testimony, but if there's no stability issue, you don't need anything.

Q. Now, how would a POSA go about trying to determine whether a given molecule has a stability issue?

A. Well, I mean, in one case you do high stress studies to try and identify potential degradation products, and you do expiration dating protocols. Again, there's general guidance. I think there's one in my book on how to do expiration dating studies, experimental design and interpretation.

There would be, you know, general guidance as to how to provide with expiration dating determination.

Q. Can we please bring up PDX 710.

THE COURT: Now you have put this thing into some kind of solution, if it is to be a parenteral, right?

THE WITNESS: Yes. For a parenteral product, yes, it is put in the liquid form.

So, here, of course, the preformulation research there's the systematic search. I mean, this is what's described in the textbooks in the chapter of the types of variables that you look at, particularly pH, temperature, concentration of the drug, what we're calling API, which that's a specific designation of something that can be, you know, FDA-approved, but the drug concentration, particular variables, and you systematically would explore those variables. And you generate the data, characterizing a

specific product and characteristics of that product and the properties of the drug molecule, and you develop what's called a preformulation and formulation report that would become part of your data package for the drug product.

BY MR. DITTMANN:

Q. Can we please bring up PTX-325. Do you recognize this, Doctor, as a textbook titled "Pharmaceutical Dosage Forms: Parenteral Medications Volume 1"?

A. Yes.

Q. If we can please turn to Page 3. Do you see towards the middle there's a date, 1992; is that correct?

A. Yes.

Q. If you can please turn to the next page, Page 4. And do we see, Doctor, this is a chapter of this book authored by a Sol Motola and Shreeram Agharkar?

A. Yes.

Q. We can turn to the second sentence under the introduction, and I'll, again, read this into the record. "Experiments are designed to generate data characterizing specific pharmaceutically important, physicochemical properties of the drug substances and its combination with selected solvents, excipients, and packaging components. These studies are carried out under stressed conditions of temperature, light, humidity, and oxygen in order to accelerate and detect potential reactions."

Do you see that?

A. Yes.

Q. Can you please explain what the Motola book chapter is referring to here?

A. Okay. In the process of developing a product you have to ensure ultimately its potency and purity. I mean, that's required in order to have marketing authorization to distribute a product, so you have to be able to ensure its potency and purity, and you have to be able to show that you can detect various degradation products in your product.

And, I mean, if you see a high level of degradation product you have to test that for toxicity, too. So you have to show that your degradation products are below a certain level. So you have to develop the analytical techniques for those degradation products, and, so, you need enough of the material to be able to develop your analytical detection techniques.

So, you generally use stress conditions, and you'll detect more degradation products than you'll see under typical pharmaceutical storage conditions, but you have to be able to detect them -- identify them and detect them.

THE COURT: And this is in the preformulation stage?

THE WITNESS: That you would do these experiments, yes, yes.

BY MR. DITTMANN:

Q. And is what we're seeing here in the Motola book chapter the sort of preformulation experiments that you were describing earlier?

A. Yes.

Q. Can we please turn back to PDX 702. I want to shift now, Doctor, into your opinions that you have provided in this case.

THE COURT: I think maybe this would be a moment for us to take a little recess. Off the record.

(Discussion held off the record)

(Brief Recess.)

BY MR. DITTMANN:

Q. Welcome back, Doctor.

Could we please have up on the screen again PDX-702. And so I'd like to now turn, Doctor, to your opinions in this case and we'll start with the first one we see here: "A POSA would have had no motivation to add a chelating agent like EDTA."

Do you have a slide summarizing your opinions on this first topic?

A. Yes, I do.

Q. Please bring up PDX-711.

And can you please explain what we see on this slide?

A. Okay. So here's the basis for my conclusions. There is no -- my conclusion is there's no motivation to add a

stabilizing agent, including EDTA. For instance, there was no indication of stability issues from the prior art. The only potentially commercially viable palonosetron formulation was disclosed in Example 13 of the '333 patent, which is silent on stability.

And so, absent any stability issue, a POSA would not have been motivated to add a stabilizing agent, and much less a chelating agent like EDTA. So that's the summary of my opinion.

Q. How did you confirm that the prior art did not disclose any stability problem with respect to palonosetron?

A. Well, I reviewed the -- the information and background provided by the defendants in this case, I think I got that right, the defendants in this case, the information that they used, and also my own literature search and knowledge in the chemical stability area, and I could not -- I did not find any -- any information regarding the stability or stability-related issues for palonosetron.

So, there's nothing in the literature prior to the 2002 to 2003 time frame regarding the instability of palonosetron that -- there's no prior art in my conclusion.

Q. And, as part of generating that conclusion, did you perform your own search, Doctor, of the prior art?

A. Yes, yes, yes. I performed --

Q. Were there -- I'm sorry -- go ahead.

A. I was going to say, I performed a literature search on palonosetron, yes, yeah.
Q. Were there any palonosetron formulations disclosed in the prior art?
A. No. I mean, I've cited here the Example 13 of the '333 patent, that would be prior art. And there was a publication of an extemporaneously on-site compounded formula in the Tang reference, in the Tang reference, a clinical reference. But, no, there was really -- this was -- this was all -- the only example in the prior art.
Q. To be clear, the example in the prior art that you did see that was a potential formulation --
A. Formulation.
Q. -- was Example 13 of the '333 patent?
A. Yes.
Q. Now, let's take a look at that patent --
THE COURT: Example 13 gives a few ingredients, right?
THE WITNESS: Yes.
THE COURT: Along with --
THE WITNESS: Compounds --
THE COURT: -- Formula I --
THE WITNESS: Yes.
THE COURT: -- which is a whole class of molecules?
THE WITNESS: Correct, correct.

THE COURT: Go ahead, Mr. Dittmann.

THE WITNESS: Correct.

BY MR. DITTMANN:

Q. And that's --

A. My understanding is, because I did explore that, that palonosetron specifically, the specific chemical identified as palonosetron is in the claims of the issue, and I think in the patents in this case, they -- they give a formula with palonosetron and the formula, or at least as part of the preformulation studies.

But you're -- but you're correct, Your Honor, that the '333 patent is -- compound has in it the compounds of Formula I, which is many compounds, I agree.

THE COURT: Compounds, plural --

THE WITNESS: Um-hum.

THE COURT: -- of Formula I.

BY MR. DITTMANN:

Q. Why don't we take a look at the Example 13 disclosure from the '333 patent.

Can we bring up DTX-343, starting at Page 15. If we could just blow up just the Example 13, the text at the top there, yes, and then on the following page, just the intravenous formulation disclosure. Thank you.

You considered, Doctor, this example as part of your analysis, correct?

A. Yes, I have.
Q. And what information did this Example 13 I.V. formulation disclose regarding the stability or instability of palonosetron solutions?
A. This patent did not disclose anything that would be relating to stability of palonosetron or any of the other compounds in Formula I. There was no information regarding -- specific information regarding palonosetron stability that a formulator could -- could use.
Q. As part of your analysis in this case, did you see any other prior art that disclosed specific palonosetron formulations?
A. No formulations, no.
Q. So is it correct that the prior art disclosed palonosetron formulation starting in -- this is a 1993 patent, correct?
A. Yes.
Q. And you've seen no other prior art up till 2003 that disclosed any instability issue relating to palonosetron solutions, correct?
A. Correct.
Q. Dr. Amidon, did you hear Dr. Kirsch testify last week that a POSA would assume that there was an instability associated with palonosetron?
A. Yes, I heard that testimony by Dr. Kirsch, yes.

Q. Do you agree with Dr. Kirsch?
A. No, I don't agree with that.
I think that a formulator is always aware of potential -- that instability is something that has to be looked for. But you would look at the prior art and if you see no information regarding instability, you'd say, well, you know, this compound, there isn't any evidence for instability of this compound, and that would be the way you would work forward, is assuming there would be no instability.
Q. And, just to summarize, was there any suggestion of instability in any of the palonosetron prior art that you've seen in connection with your analysis in this case?
A. No, there was no evidence in any prior art of any instability.
Q. With no prior art disclosure of an instability issue for palonosetron, do you understand that Dr. Kirsch relies on documents relating to other molecules to draw inferences relating to palonosetron's stability properties?
A. Um-hum. Yes.
Q. And, specifically, do you recall Dr. Kirsch testifying that a Won 1995 publication, which is DTX-345, would alert a POSA to the possibility that palonosetron was susceptible to oxidation?
A. Yes, I recall -- I recall Dr. Kirsch testifying to that, yes.

Q. And do you agree with Dr. Kirsch?
A. No, I do not.
Q. Why not?
A. Well, I prepared a few slides to illustrate why the compound in the Won publication would not be relevant to a POSA looking at palonosetron, so -- this kind of gets kind of technical.
THE COURT: For stability purposes?
THE WITNESS: For stability purposes, yes. This gets kind of technical, Your Honor, but ask questions if you have any questions.
THE COURT: Okay.
THE WITNESS: But, yeah, so we've looked at the structures and the chemistry here, and I do not agree with Dr. Kirsch.
BY MR. DITTMANN:
Q. So why don't we take a look at the demonstrative you've mentioned starting with PDX-712.
A. Yes.
Q. Can you explain what you see here, Doctor?
A. So, here I've highlighted in the chemistry -- the chemical, the element difference between the Won compound which is RG 12915, that's the compound that Dr. Kirsch referred to, and here's the palonosetron.
You can see that the chemical difference here, this is

a cyclic lactam versus a linear lactam, and you have a benzofuran here. You do not have that. And you have cyclohexane with a fairly rigid structure here -- I'm sorry.

THE COURT: Can you slow down just a little with the words.

THE WITNESS: I'm sorry. Okay. Where do you want me to back up to?

Okay. So that this is a linear amide, and this is a cyclic lactam, this is a cyclic amide, a more rigid structure indicated by the -- the dash lines here indicate the stereochemistry of this molecule that's not indicated here. Because there isn't stereochemical issues here in this molecule, but these there are.

And you can see the difference in the chemical structures in this two-dimensional representation of the chemical structure. So the chemistries of these two molecules are quite different.

BY MR. DITTMANN:

Q. Now, Dr. Amidon, just to make the record clear, if we could, going back to the Won molecule starting on the left, the top part of the molecule, here, can you explain with the O, H, and N, next to the --

A. So this is --

Q. Can you explain what that is again?

A. Okay. Well, this is the bonding -- this is what would be

called a linear amide. This is an amide. And this is an amide, too, but it's connected to a cyclic. It's a cyclic amide, so we call this a lactam, most common --

THE COURT: That's on the palonosetron side?

THE WITNESS: In the palonosetron, it's a cyclic lactam. I mean, this is a six-membered lactam. I mean, the lactams are famous, beta-lactam antibiotics, but this is not anything like that.

But this is a cyclic amide, a very unique structure, as opposed to the linear amide here. This is the amide bond and this is the amide bond here.

BY MR. DITTMANN:

Q. It may be helpful if we can bring up PDX-713 and continue our discussion.

A. Yeah, okay.

So, I think Dr. Kirsch was highlighting this similarity, and that is true, obviously. There is a quinuclidine -- well, okay, this is a tri- -- we'll get into this, but this is a triamine, but it's a particular quinuclidine, and that part of the molecule, just that part, highlighted in the light green is the same.

THE COURT: In both?

THE WITNESS: In both molecules.

THE COURT: In both molecules?

THE WITNESS: Molecules, yeah.

But the -- the rest of the molecules are quite different.

And so the chemistry is, of course, highly dependent on the actual chemical structure and chemical bonding. So these are quite different molecules.

BY MR. DITTMANN:

Q. Bring up PDX-714.

THE COURT: The fact that you've got a ring, a ring structure in the palonosetron, connecting up -- please forgive me. I'm not a chemist --

THE WITNESS: I -- I --

THE COURT: -- the O, the N, and the H.

THE WITNESS: Yes.

THE COURT: You say that that's a -- that's a tighter structure than the linear one that the Won has connecting those three atoms?

THE WITNESS: Yes, yes. It's more rigid, it's more structurally fixed spatially, yes, because of the bonding structure of carbon and nitrogen, yes.

BY MR. DITTMANN:

Q. And do you have a slide discussing this rigidity you're mentioning?

A. Yes, I think I've illustrated that on another slide.

Q. Can we bring up PDX-714?

Can you discuss what we see here, Doctor?

A. Yes. So, here, it's kind of summarizing that point, Your Honor, here. This is a more flexible, you're going to have cis and trans, this quinuclidine versus the hydrogen, this part.

THE COURT: You have what?

THE WITNESS: I'm sorry. Okay.

BY MR. DITTMANN:

Q. Doctor, what might be helpful if you --

A. I'm sorry.

Q. -- point to the left side, and say, we're talking about Won and then we'll move to the right side next. Is that okay?

THE COURT: Yeah. We have two things we're contending with here. We're making a record, so the pointer, when it's on, one --

THE WITNESS: You don't -- yeah.

THE COURT: -- one drawing or another, the words have to say, now I'm comparing what we see here on the left with what we see here the right. And the other, of course, is the comprehension, the communication gap.

THE WITNESS: Okay. Okay. Well, just slow me down.

THE COURT: And also, the other thing is that the court reporter has to be able to get these words down.

THE WITNESS: I understand. I understand. Just slow me down.

THE COURT: Just take your time.

THE WITNESS: This is not an environment I'm used to teaching in so...

So, on the left, with the Won compound, the RG 12915, this structure is free to move, in fact, the hydrogen and this carbon can change position and we call it cis/trans. And so this is more flexible here. While this cyclic structure fixes this nitrogen in a chemical position. Okay? So that was my -- that was the essential point of that.

THE COURT: Okay. And you've used the term "flexible" for the Won at that location, and "rigid" for the palonosetron at that location?

THE WITNESS: Correct. Correct. Correct.

And then I highlighted here also that there's different elements. There's a chlorine and an oxygen in the Won compound, which would make the chemistry of the Won compound quite different.

So, in conclusion, this is maybe getting a little technical, but the Won -- the compound on the left, the Won compound, is a different chemical structure than the palonosetron, and so a POSA would look at it and say, it's not much help to me with regard to predicting palonosetron properties.

THE COURT: Including stability?

THE WITNESS: Including stability.

THE COURT: Okay.

THE WITNESS: The stability is very dependent on the electronic structure and the elemental structure of the molecule.

BY MR. DITTMANN:

Q. Just to take one step back, Doctor, to make sure that the record is clear, you were talking about the chlorine and oxygen on the Won molecule, if you see on the left side of the demonstrative, and we see here there are labels "activator" next to both. Can you explain what you mean by "activator"?

A. Well, there's -- for chemical reactivity, there would be more reactive, more chemically reactive.

Chlorine has got more electrons around it as an atom and oxygen has got two -- lone pairs, so there's more electron -- lone-pair electrons. Lone-pair electron, that's a function of the bonding structure of chlorine and oxygen. So there's more electron freedom, more electrons free in the oxygen and the chlorine.

So activator is -- that's just illustrating that these compound -- the Won compound on the left with the chlorine and oxygen is electronically a very different structure than the palonosetron compound on the right.

BY MR. DITTMANN:

Q. So, turning to the palonosetron on the right, do you see any such activators present in the structure of that molecule?

A. No.

Q. Now, just to summarize, what -- where we are so far, you know, what would a POSA infer, if anything, with respect to stability looking at the structural differences between these two molecules?

A. I believe that the Won compound on the left would be of no help, so there'd be no useful information from the Won compound that you would extrapolate to the palonosetron compound. So I would say you would learn nothing about palonosetron from the Won compound.

THE COURT: Now, Doctor, this drawing, chemical drawing of the palonosetron molecule, doesn't show up in the '333 patent. That's what we've heard so far in the evidence. Would you agree with that?

THE WITNESS: The chemical -- okay.

THE COURT: Chemical drawing.

THE WITNESS: The chemical drawing of the Won compound on the left is only generically included in the '333 patent.

THE COURT: But I'm talking about the palonosetron on the --

THE WITNESS: I'm sorry, the palonosetron, okay. The palonosetron compound in the '333 patent, I'm sorry. I was confused, Your Honor.

Correct, the palonosetron compound in the '333 patent is included only in the generic Formula I with the A, B, Cs

and the symbols that they have in there.

If you assemble -- if you look into that in all of the potential compounds, you will find palonosetron is one of the compounds in that -- that's contained in the structures that were in the '333 patent.

THE COURT: That I get.

THE WITNESS: Yeah.

THE COURT: I just wanted to establish, you've looked at the '333 patent, and this chemical drawing of the palonosetron molecule is not drawn in the '333 patent. But what we've learned so far in the evidence here, I just want to check with you on this, the actual palonosetron molecule is verbally described in the '333 patent, it is called out and described.

THE WITNESS: That's my understanding, it was called out and described but not structurally presented, yes.

THE COURT: Okay.

THE WITNESS: Yeah.

BY MR. DITTMAN:

Q. Do you understand that Dr. Kirsch relies on a Clark 1993 reference, DTX-282, in asserting that those -- the prior art recognized similarities between the Won molecule and palonosetron?

A. Yes, I'm familiar -- I'm aware of that testimony, yes.

Q. And do you understand Dr. Kirsch has contended that a

POSA would have focused on the Clark 1993 for whatever information they can glean about compounds that are related to palonosetron that may inform them about their efforts to develop a stable palonosetron formulation?

A. Well, I think a POSA might -- might have been aware of the Clark reference, but the Clark reference was focused on developing a pharmacophore model and used crystal structure, so I think it would be of little assistance. But I think I have some transparencies on that, but I did look at the Clark article and I think it does not say anything regarding chemical stability.

Q. Can we bring up the Clark reference, DTX-282? And, first, if we can focus on the abstract. Thank you.

Can you -- I think you started to summarize this, Doctor, but can you explain to the Court what Clark 1993 was focusing on?

A. Well, okay. There's a lot of technical chemical details in here.

I would just point to the last line in the abstract. Computer modelling here, computer modelling studies were performed, and previously forward -- previously reported 5-HT_3 receptor antagonists -- previously reported -- I'll speak more slowly -- 5-HT_3 receptor antagonist pharmacophore models were refined to include a lipophilic binding domain.

So this was focused -- this was focused on a

pharmacophore model -- models which was research -- a research effort in the 1990s to try and reverse engineer a receptor, and they're looking for 5-HT receptor antagonists, things that bind to this receptor. And they wanted to reverse engineer what the receptor looked like.

It's -- it was not a very successful line of research, but that's what this paper -- my point is, this paper focused on a pharmacophore model and based on the crystal structure of the molecules. So it had little -- little applicability to solution conformation which would be more freedom in the solution than in the solid state. So this -- this paper is of, I would say, no help to a formulation scientist.

Q. Just to be clear, was Clark 1993, in your view, addressing any stability-related issues?

A. No.

Q. Can we turn to Page 5, please. I want to focus on the right column, yeah, you have it there, correct.

A sentence I'll read into the record that states: "In fact, a crystal structure of another 5-HT_3 antagonist (44) has the conformation of the quinuclidine ring system in a similar conformation to the overlap conformation of (S,S)-37." Do you see that, Doctor?

A. Yes.

Q. And, first, do you understand this to be a sentence that Dr. Kirsch focused on in his testimony?

A. Yes. This is my understanding that the sentence that -- that Dr. Kirsch referred to, and the sentence particularly focuses on the quinuclidine part, just that upper right-hand part of the molecule. And those two, the -- that's a tricyclic with a nitro- -- bridge nitrogen, that's a very fixed structure, so this is not really saying anything other than that's fixed. That's the same in the two molecules.

Q. Just for context, if we can bring up the structures below that sentence, just to make sure we're all following along.

A. Yeah. This is the quinuclidine part.

Q. So you're pointing to the upper right portion of the molecule?

A. Yes.

Q. Compound 44?

A. Yes.

Q. Okay. If you go back to --

THE COURT: With the jagged line through it?

THE WITNESS: Yes, that means it's a tricyclic. This is the cycle, this is a cycle and this is -- this is a very rigid structure that you can do. Six-membered rings are common in organic chemistry.

BY MR. DITTMANN:

Q. Now, in the sentence we were looking at from Clark 1993, 44 is a reference to this Compound 44 shown below, the text we're looking at?

A. Yes, that's the Won compound.
Q. And we know that because it says RG 12915?
A. Yes.
Q. And do you also understand that the reference to (S,S)-37 is to palonosetron?
A. Yes. That's indicating -- S,S is indicating the stereochemistry of the palonosetron molecule.
Q. With that context -- and thank you, Doctor -- can you explain what a POSA in your view reading this sentence we see here on the screen from Clark 1993 would understand it to be saying?
A. It's just saying that the quinuclidine part is in a similar conformation to the overlap conformation of the S -- (S,S)-37. So it's saying this part of the molecules are the same or have a similar conformation. I don't think that surprises anyone.

And this says in the crystal structure, which is not the solution structure, and I've pointed out that this section of the molecule is more flexible in the RG 129 -- I'm sorry, yeah, 12915, so this is more flexible.

THE COURT: The NH section?

THE WITNESS: Yes, than the corresponding structure in palonosetron.

THE COURT: And this article was looking at binding affinity to the receptor, right?

THE WITNESS: Correct, yes. Correct, correct.
BY MR. DITTMANN:
Q. And so, Doctor --
A. It has nothing to do with chemical stability.
Q. So, Doctor, by conformation, do you understand that to be referring to the arrangement of the molecule when it's present in a solid crystal?
A. Yes, yes.
Q. And, again, as you explained, the fact that the sentence uses the words "crystal structure" tells you they're talking about comparing the conformation of one part of the molecule, palonosetron, versus the Won molecule when in the solid state?
A. Yeah, that -- that part of the molecule, yes, correct.
Q. Could we please --
THE COURT: If you drop it into solution, though, the molecule, if it doesn't fall apart, is still in the same conformation, right?
THE WITNESS: One of the conformations, presumably. It's a function of the energetics, and in the solid state, the molecule has to interact with other neighbor molecules that are in fixed positions, so that tends to fix the conformations in the solid state, whereas in solution, it's surrounded by solvent.
For example, water molecules, they can hydrogen bond here and here, and so the solution conformation is much more

flexible. And the molecule, the chemical bonds can rotate. So it has more freedom in solution than in the solid state.

THE COURT: Kind of floating around in there and it's -- it's --

THE WITNESS: Flexible.

THE COURT: It's 3D aspect?

THE WITNESS: Correct, it's -- right, yeah.

THE COURT: Can rotate?

THE WITNESS: Correct, yes, yes.

BY MR. DITTMANN:

Q. And so just to make sure we're following, Doctor, in the solid or crystal form, the Won molecule would be fixed in terms of its conformation, correct?

A. Yes.

Q. And, as you explained, in the solution state, the Won molecule's flexibility that you discussed earlier would become more relevant with respect to stability issues, correct?

A. Yes.

Q. Now, can we turn back to PDX-713 for a moment?

And if you could, Doctor, again, since we're talking about this quinuclidine structure that's present in both Won and palonosetron, can you remind us, using this slide, what you're talking about here in terms of the differences you might see in terms of behavior of these molecules in solution versus the solid state that Clark was talking about?

A. Well, okay.

To summarize, I think this part of the molecule, the quinuclidine part, this is a rigid structure, in green, while the bonding to the rest of the molecule here, this is fixed. This is, again, a cyclic structure, whereas here, it's more flexible.

So the solution conformation, the three-dimensional conformation in solution, would be different for the Won compound on the left and the palonosetron compound on the right. But, as I've said, this has little to do with, well, chemical stability.

MR. DITTMANN: Your Honor, just -- we can keep going. I know you said you had a call at 3:30. We can keep going or we can take a break. It's up to you.

THE COURT: We could take a break now.

(Break taken.)

THE COURT: Back on the record.

BY MR. DITTMANN:

Q. So, Dr. Amidon, just to close the loop --

THE COURT: Off the record.

(Discussion off the record.)

THE COURT: Back on the record.

BY MR. DITTMANN:

Q. Dr. Amidon, to close the loop on the Clark 1993 reference we've been discussing, what, if anything, in your opinion

would a POSA have learned about the chemical stability of either palonosetron or the Won molecule from reading the passage we were focusing on?

A. I would say the Clark publication does not provide any information regarding stability of either of the compounds. The Clark paper was interesting from a scientific point of view, as pharmacophore and receptor binding, but not for chemical stability.

Q. And would a POSA have assumed any similarities in the chemical stabilities of either molecule based on the Clark 1993 reference?

A. No.

Q. Now, did you hear Dr. Kirsch during his testimony refer to the quinuclidine structure we've been discussing, the one that's on the upper right-hand part of the molecules, as a tertiary amine?

A. Yes, I heard that testimony.

Q. And did you also hear Dr. Kirsch contend that tertiary amines were known to easily oxidize?

A. Yes, I heard that -- that statement by Dr. Kirsch.

Q. And do you agree with Dr. Kirsch?

A. I think that's a wild extrapolation. And so I would address that, specifically, the textbook reference that Dr. Kirsch had, and that's written into an Organic Chemistry textbook, synthesis textbook, which I think I have a

demonstrative on.

Q. Let's -- let's take a look at the reference you're referring to, Wade, DTX-344. Is this the Wade reference you were just --

A. This is the Wade reference that I was -- that Dr. Kirsch referred to which I looked at. It's an Organic Chemistry synthesis book, yes.

Q. Can we please turn to Page 38 of Wade? I'm sorry, 36. And I want to focus on towards the top of the page, that first paragraph, yes, thank you.

And I'll read into the record the first sentence: "Amines are easily oxidized, and their oxidation is frequently a side reaction in a synthesis, or even in storage in contact with the air."

Do you see that?

A. Yes, I do.

Q. And do you understand that to be the sentence that Dr. Kirsch focused on in his testimony?

A. Yes, that's, I think, the sentence in Dr. Kirsch's testimony, yes, and I think that's organic synthesis, and actually, pharmaceutically, we don't use free amines. We use the salts, and palonosetron hydrochloride is the salt we use, and I think the next sentence states that.

Q. Why don't I read that in for the record. The second sentence states: "Preventing air oxidation is one of the

reasons amines are commonly converted to their salts for storage or use in medicines."

Do you see that?

A. Correct, yes.

Q. Can you explain how a POSA would have understood that second sentence, what was it referring to?

A. Well, that's the reason we use salts, hydrochloride salts, in developing pharmaceutical products.

And the oxidation of amines in chemical synthetic pathways is done under conditions to maximize the chemical yield of some synthetic procedure versus, that's very different than what we're trying to do to stabilize a compound for -- in a pharmaceutical product. So I don't -- this statement has -- of no use to a formulator.

Q. To make sure we're all following, Doctor, if you look at the word "converted" in the second sentence of Wade we've been looking at?

A. Yes.

Q. By "converted," are you referring to these reactions where you intentionally want to create, for example, a salt for storage or use in medicines?

A. Yes, yes.

Q. And that's different from whether or not a pharmaceutical molecule will just undergo potentially oxidation without an intentional reaction being performed on it?

A. Okay. I think -- okay, that was a fairly long statement, but by -- by converting the amine, the nitrogen, to a protonated nitrogen with a hydrochloride, an acid like hydrochloric acid, you generate a different chemical bonding structure to nitrogen, it becomes tetrahedral as opposed to planar, and that --

THE COURT: P-L-A-N-A-R?

THE WITNESS: P-L-A-N-E-R, planer.

So that the -- the nitrogen is much more stable in the hydrochloride form or the hydrogenated form. And so that's what we use.

We use a lot of salts as pharmaceutical APIs, and most of our amines are hydrochlorides or some other salt that is used as the actual active pharmaceutical ingredient.

THE COURT: When we look at the patents, they call for palonosetron hydrochloride, I think; is that right?

MR. DITTMANN: That's the salt form of the active ingredient of Aloxi®, yes, Your Honor.

THE COURT: Is that right, Doctor?

THE WITNESS: Yes, yes, yes, yes.

THE COURT: Is that what you're talking about?

THE WITNESS: That's -- yes, that's correct. That's what we're talking about and that's -- that would be -- that's what a POSA would expect, hydrochloride salts or maybe another salt, could be, you know, a mesylate salt or something, but,

yes. Hydrochloride salts are very common in pharmaceutical APIs.

BY MR. DITTMANN:

Q. And, Doctor, the -- this Wade reference we're looking at, this organic synthesis textbook, in your view, would a POSA view this reference as useful for determining whether there are potential stability issues with respect to formulation products?

A. No, this -- this reference is for organic chemical synthesis, so it would not be of help to -- to a POSA with regard to stability. I mean, a POSA would know, okay, amines can oxidize. I mean, they would know that. But this reference, we deal with hydrochloride salt, so it's something that a POSA would be aware of. But you would have to get the evidence with the specific compound that you're studying, so...

THE COURT: Back to the chemical drawing that we were looking at for the palonosetron with the quinuclidine --

THE WITNESS: Okay. Very good. Okay.

THE COURT: -- component, is that expressed in terms of its form in a salt or just in its basic molecular structure?

THE WITNESS: The -- yes. This would be the nitrogen here that would be protonated. So, yes, the salt would be associated with this nitrogen. This amide nitrogen is not

really very basic. So this would be the protonated form, likewise here, yes. So it would be with this part of the molecule that would be the salt.

THE COURT: Referring to the nitrogen in the quinuclidine --

THE WITNESS: Quinuclidine ring, yes.

THE COURT: -- ring?

THE WITNESS: Yes.

BY MR. DITTMANN:

Q. And, for the record, we're looking at PDX-713 in the right side of the palonosetron molecule, correct?

A. Right, correct, right, yeah.

THE COURT: So if it's in a salt form, does it change the chemical drawing?

THE WITNESS: No, because this is already tetrahedral, so it's got three functions there. The propanone would go into this position.

I mean, we get into some bonding chemistry, you know, sp^3 type hybridization, you know, molecular orbitals, but the proton would go here, so it would not change this tricyclic bonding of nitrogen.

BY MR. DITTMANN:

Q. We can turn back, please, to the Wade reference, DTX-344. And if we can bring back up the text but also the figures below it, thank you.

I think, Doctor, you were alluding to having to focus on structures, and can you confirm for me, looking at the structures we see below the Wade sentence we've been focusing on, do any of them have the specific quinuclidine structure we've been discussing relating to Won and palonosetron?

A. No. There's no quinuclidine structure here. These are various types of amines, and the quinuclidine structure is a very unique or particular structure, not illustrated here in this textbook.

Q. Are you aware of any examples of compounds having tertiary amine structures that do not undergo oxidation in solution?

A. Well, we have many amine compounds in -- as active pharmaceutical ingredients, and I've selected a few that are not chemically unstable -- or chemically stable, I should say.

Q. Can we please bring up PDX-715.

Can you explain what we're seeing here, Doctor?

A. Yes. So here I have chosen four, in this case, known tertiary amines, but they're -- actually, two are quinuclidine, and two are tertiary amines, although they're part of a cyclic structure.

These four compounds, amines, are -- they're not known to be unstable. There's no evidence for instability of any of these four compounds. And we have many more amines. I'm going to say one-third of our APIs in pharmacy are amines.

Hydrochlorides typically are not unstable.

Q. Now, first, for reference, do you understand these four molecules we see on PDX-715 to be setrons that were already marketed in various countries long before 2003?

A. Yes, these were on the market with no known instability problems, yes.

Q. Do any of the compounds we're seeing here have the quinuclidine structure like we see in palonosetron?

A. Well, yeah. These two, and the portion highlighted by -- with the dashed box here. This is the quinuclidine structure, as is -- this is -- has an oxygen here for dolasetron, but this is the quinuclidine-based structure here.

THE COURT: Referring to the upper two figures?

THE WITNESS: Yes.

BY MR. DITTMANN:

Q. You're referring to azasetron and dolasetron on the figure?

A. Yes.

Q. Was there any information in the prior art suggesting that either azasetron or dolasetron underwent oxidation when in solution?

A. No, there was no information in the prior art regarding any oxidation susceptibility of those compounds.

Q. And, moving to the bottom two molecules, tropisetron and granisetron, is it correct that both of these molecules have

tertiary amines in their structures?
A. Yes.
Q. And are you aware of any prior art that reported either of these molecules to undergo oxidation in solution?
A. There is no prior art indicating these molecules were unstable or susceptible to oxidation.
Q. To sort of summarize where we are so far, Doctor, is it your opinion that Dr. Kirsch's oxidation theory based on a comparison of palonosetron to the Won molecule is flawed?
A. Yes.
Q. And are you aware of any prior -- prior-art information that would have led a POSA to believe that palonosetron was susceptible in any respect to degradation?
A. I'm not aware of any prior art indicating that palonosetron would be susceptible to oxidation.
Q. Now, Dr. Amidon, if a POSA was evaluating a drug candidate and did not suspect any degradation such as oxidation, would the POSA add a chelating agent like EDTA into the formulation?
A. No, no. I mean, you have to have evidence that you need an ingredient. The keep-it-simple principle that we've referred to earlier in formulation is the guiding principle almost -- that's the golden rule. So, without evidence that you need a chelating agent, you would not include one.
Q. If we could bring up, please, the testimony from June 5th

at Page 40, Lines 14 to 25. And if you can bring up the question actually as well.

First, Dr. Amidon, do you understand that Dr. Kirsch gave testimony relating to this golden rule or guiding principle that we've been discussing?

A. Yes.

Q. And he discussed that the context of the Broadhead 2001 reference we discussed earlier?

A. Yes.

Q. Now, do you understand Dr. Kirsch, in his testimony he provided, to be agreeing or disagreeing with your view of this golden rule or guiding principle in designing parenteral formulations?

A. Yeah, I think this agrees with -- with the guiding principle of a formulation scientist. I think Dr. Kirsch --

Q. I'm sorry. I think we have the wrong page up. Page 163. Sorry.

I'll read it into the record, Doctor, to make it simpler, Lines 7 to 13. So I'll read this into the record.

"Now, a formulator's goal will always be to develop the simplest formulation with the fewest excipients possible, correct?

"ANSWER: In -- yes. I mean, that's correct. Any excipient that's placed in an injectable product has to be justified.

"QUESTION: It has to be justified?

"ANSWER: That's correct."

So with that, Doctor, do you understand Dr. Kirsch to be agreeing or disagreeing with your view of the --

A. I think --

Q. -- golden rule we've been discussing?

A. I think Dr. Kirsch is following the rule of formulators as you keep it simple and you justify what you add to a product.

Q. Can we please bring up DTX-278? And we see this is a textbook titled Pharmaceutical Dosage Forms: Parenteral Medications, and I think we saw a portion of this previously?

A. Yes.

Q. Please turn to Page 3. We see, once again, this is dated 1992, correct?

A. Yes.

Q. And turning to Page 23 -- I'm sorry.

Could we go back to the -- the beginning of the chapter, which I believe is Page 4, just to frame our reference there.

We see this is a Chapter 5 titled Formulation of Small Volume Parenterals by Patrick P. DeLuca and James C. Boylan.

Do you see that?

A. Yes.

Q. Now, please, if we can turn to Page 23. And I want to

look at towards the bottom, there is a heading, Added Substance.

And I'll read into the record the first sentence we see here: "Added substances such as antioxidants, buffers, bulking agents, chelating agents, antimicrobial agents, solubilizing agents, surfactants, and tonicity-adjusting agents must frequently be incorporated into parenteral formulas in order to provide safe, efficacious, and elegant parenteral dosage forms." And it continues, "Any additive to a formulation must be justified by a clear purpose and function."

Do you see that?

A. Yes, I do.

Q. And do you agree that these two sentences reflect the state of the art of formulation design in 2003?

A. This -- yes, yes. This is -- this is the basis that a POSA formulator would operate under. This would be their principle of operation, yes.

Q. Okay. If we can go back to Page 4 again, the beginning of this chapter. And we see, again, one of the authors, do you recognize Patrick P. DeLuca to be one of the experts who has provided testimony on behalf of defendants in this case, or will be?

A. Yes, I recognize, I know Dr. DeLuca and I also know Dr. Boylan, so...

Q. Shifting gears a little bit, Dr. Amidon, do you recall hearing Dr. Kirsch testify that routine preformulation studies would have led a POSA to pursue the claim formulations?
A. I recall that testimony, yes.
Q. And do you recall Dr. Kirsch ever discussing any actual preformulation data relating to palonosetron during his testimony?
A. I don't recall Dr. Kirsch referring to any preformulation data in his direct testimony.
Q. Now, what palonosetron preformulation data, if any, was disclosed in the prior art?
A. None.
Q. Can we please go back to PDX-706.

Now, again, this is the legal standard that you applied, Doctor?
A. Yes.
Q. And do you understand this routine preformulation data to be a proper part of an obviousness analysis?

THE COURT: You mean coming up with some?

BY MR. DITTMANN:
Q. I mean considering it, since it's not in the prior art.

Do you understand that the -- any preformulation data is properly considered as part of the obviousness analysis in this case?
A. I'm not sure --

THE COURT: I don't understand the question.

THE WITNESS: I'm not sure I understand it either.

BY MR. DITTMANN:

Q. Sure.

So, we just discussed, Doctor, that you didn't see any palonosetron preformulation data in the prior art, correct?

THE COURT: It was taking place secretly in a lab.

BY MR. DITTMANN:

Q. Correct.

A. Yes.

THE COURT: Development lab.

THE WITNESS: Yes.

BY MR. DITTMANN:

Q. And applying the test that you've used, do you see that you must consider the differences between the prior art and the claims at issue, correct?

A. Correct, yes.

So, I think -- my understanding is that the preformulation data, which was confidential data, was not part of prior art. But my -- my -- but formulation is so compound-to-compound dependent that every API is different and has to be studied on its own.

Q. Now, for my next series of questions, I just want to make sure we're all clear.

I want you to assume hypothetically that these

preformulation studies that Dr. Kirsch referenced, I want you to assume that they would be relevant to the obviousness analysis. Okay?

A. Okay. Okay.

Q. Now, have you seen -- in the course of your analysis in this case, have you seen actual data from the preformulation studies that were performed confidentially relating to palonosetron?

A. Yes, I have.

Q. And what was the source of these preformulation data?

A. I think the ultimate source was Syntex preformulation reports and formulation reports. Yeah, I think that was the ultimate source.

Q. Could we please bring up PTX-233.

Can you tell us, Doctor, what is this document?

A. Okay. This is, my understanding, a declaration made by Dr. Daniele Bonadeo of Helsinn, made to the Patent Office during the patent prosecution. And it refers to or brings -- or reports data that was in the Syntex preformulation or formulation reports.

Q. Okay. And do you understand Daniele Bonadeo to be one of the inventors of the patents-in-suit?

A. Yes.

Q. Can we please turn to the second page.

Towards the bottom, you see this is a declaration dated

June 8th, 2009?
A. Yes.
Q. So this is after our 2003 date that we're talking about for your analysis, correct?
A. Yes. Although I think it reports data that was done in the 1990s but -- yes.
Q. Data that was confidential --
A. Yes.
Q. -- as of 2003?
A. Yes.
Q. Now, can you explain, what does this document, PTX-233, disclose?
A. I think it discloses some unique properties of the palonosetron compound.
Q. And did you review the data set forth in this Bonadeo declaration, PTX-233?
A. Yes.
Q. Can we please bring up Page 5. I want to focus on some of the data in a little bit of detail.

But, if we can first, to get our bearings, can you tell us what this table is reporting? What type of an experiment are we looking at?
A. Yes.

So, this is chemical stability of palonosetron, in this case, performed at pH 7.4 under air as a function of drug

concentration in temperature.

So this is a typical preformulation result, and you can see that the temperatures here in the left-hand column from 5 degrees centigrade room temperature up to 100 degrees centigrade, which is actually boiling water, that's 212 degrees Fahrenheit, so this is a very wide temperature range.

And then they report the stability, the percent drug remaining, and you can see that, even after eight weeks, even at a very high temperature, the drug is very stable.

Okay. And then --

Q. We're going to get to that, Doctor, in a moment, but can you first explain, why are different temperatures being looked at in connection with this table?

A. Well, of course, I would say the way a POSA would look at this is that the temperatures 40 and 60 degrees are part of the stability protocol, while the higher temperatures are to force degradation to try and identify degradation products. And the concentration range here, you can see at the low concentrations, the -- the compound is very stable, even at the very high temperature.

This table goes up, I think, to higher concentrations which also -- which has some unusual data -- unusual results, I should say.

Q. So, if we can take a step back for a moment and look at the entire table to get our bearings, we have five different

concentrations that were studied, correct? 0.01 milligram per milliliter, 0.1 milligram per milliliter, 1.0 milligram per milliliter, 10 milligram per milliliter, and 50 milligram per milliliter, correct?

A. Yes.

Q. And for each of these concentrations, there are six different temperatures that were studied, correct?

A. Correct, yes.

Q. Starting at 5 degrees Celsius, right?

A. Um-hum.

Q. And RT, what does that mean?

A. Room temperature.

Q. And all the way up to, as you mentioned, boiling conditions --

A. Boiling point of water, yes.

Q. -- a hundred degrees Celsius?

A. Yes, yeah, yes.

Q. Now, to help us get some context here, can we please bring up PTX-295?

And is this correct, Doctor, this document is your Chemical Stability of Pharmaceuticals book?

A. Yes.

Q. This is the same book that we saw --

A. Yes.

Q. -- in physical form earlier?

A. Yes.

Q. Can we please turn to Page 153? And I'd like to blow up the Table 7.5.

And can you explain what this table in your book is summarizing or explaining?

A. Yes.

This is a typical stability protocol, typical stability sampling procedure. This is a function of temperature, including high relative humidity, 50 and 80 percent, because bathrooms are often high relative humidity, and you can see up to 60 degrees this is a typical expiration, looking at pharmaceutical stability, and you can see the samples are spread out here.

At lower temperatures, products are more stable, so you have sample here, this is 60 months, that's what, five years, I guess. But at the, like, 60 degrees, you only sampled for -- for two or sometimes three months because at 60 degrees, the reaction rate is three to the third -- okay, 30, 40, 50, 60 -- okay.

Based on reaction-rate changes with temperature, which are discussed in the textbook, two months' stability at 60 degrees would equate to about three years' stability at room temperature. That's an estimate.

So you sample here only over a short period of time at the high temperatures. You typically don't go much higher,

sometimes you do, for -- but because you can have physical, chemical changes like something might melt and change the physical chemistry very dramatically. But, so, this is a typical protocol.

In the --

THE COURT: Doctor, what is room temperature in Celsius?

THE WITNESS: Around 20 to 25 degrees.

THE COURT: Thank you.

THE WITNESS: Yeah. So this is approximately room temperature here. Yeah.

BY MR. DITTMANN:

Q. To make sure we're all following, Doctor, this table is talking about how you might test a pharmaceutical product to assess how stable it is and how long it may be able to maintain sufficient potency, correct?

A. Correct, correct.

Q. And, for example, at the 60 degree Celsius temperature, you may -- you would assess that for two months, correct?

A. Two months, yes. So, this allows you to get a very early estimate of what your product might be like in terms of expiration dating.

Q. Now, one question I have is, we saw the previous table in the Bonadeo declaration had data at 80 degrees Celsius and the boiling point temperature, 100 degrees Celsius. Can you

explain why we don't see this on your table in your book?

A. Going to 80 or a hundred degrees is -- speeds up the reaction. It can also change the physical chemistry, like a compound might melt, sometimes it will sublimate and evaporate. The physical chemical changes, the reaction mechanism may change, likely will change.

So, at the very high temperatures, it's used to identify potential degradation products. So, because you need to get enough of a degradation product in order to be able to identify it and then make it and quantify it analytically, you use a very high temperature to generate a lot of degradation product.

But for expiration dating for chemical -- for pharmaceutical stability, you would do a protocol like this. Ultimately, you have to study at room temperature, because that's the regulatory requirement.

THE COURT: You used the term "degradation product."

THE WITNESS: Yes.

THE COURT: And the -- Ms. Zahavi talked about it in her deposition excerpt that we saw, degradation products.

THE WITNESS: Okay.

THE COURT: But it hasn't been defined yet for us. What do you mean by it?

THE WITNESS: Okay.

THE COURT: Because it's material in this solution,

right?

THE WITNESS: Yes, yes. And it could be in the -- if the compound -- if the API reacts with something, let's say an excipient, and forms a new chemical compound, that would be a degradation product. And you have to identify what that is in your formulation. And then you have to quantitate it and be sure that that level stays below a certain value, like 1 percent or .1 percent, in order to have a shelf life.

Your product has to stay within certain defined potency, dose, and degradation products below a certain level, in order for it to be called stable to that -- to that point in time.

THE COURT: So it's like, kind of like waste material that occurs? In other words --

THE WITNESS: Yes.

THE COURT: -- all I've learned so far about stability testing is you test at the end of your ultimate end to see how much palonosetron the API is left in there.

THE WITNESS: Um-hum.

THE COURT: But you are saying that you actually test the overall solution to see if you can tease out, tease out of it some additional material that's not what you put into it?

THE WITNESS: That's correct. You do.

THE COURT: Okay.

THE WITNESS: You do. Because, well, you have to

ensure that your product has the potency, the dose that it's labeled at --

THE COURT: Um-hum.

THE WITNESS: -- but you have to also show that any other degradation product is below a certain level because the degradation products can be toxic.

THE COURT: You mean, impurity in there, right?

THE WITNESS: Yes, or an impurity from the synthetic pathway, yes. So you have to show that they're all below around the .1 percent level.

THE COURT: Okay. So you are looking in there for these --

THE WITNESS: Anything, yes.

THE COURT: -- degradation products?

THE WITNESS: Yeah.

THE COURT: Not just for how much palonosetron is left?

THE WITNESS: Right, yes. And you have to find out what they are.

THE COURT: Okay. Got it.

BY MR. DITTMANN:

Q. So, again, the 80- and 100-degree Celsius temperatures are used to identify degradant products that you might want to look out for in your stability studies, correct?

A. Correct, correct, yes.

Q. And, according to your book, you would want to assess whether a particular pharmaceutical formulation will have sufficient stability, you do that by looking at temperatures up to 60 degrees Celsius, correct?

A. Yes, typically, yes.

Q. Can we turn back to the Bonadeo declaration we were looking at, PTX-233? Thank you.

So, now, I want to focus on the 1 milligram per milliliter, at the middle concentration. We'll start with that one first, Doctor. And could you tell me how a POSA viewing this data would have viewed the stability of 1 milligram per milliliter palonosetron solutions?

A. A POSA would look at this to say, this compound is very stable because there was no degradation at 40 and 60 degrees or even at 80 or a hundred which are extreme. So this compound in eight weeks at 60 degrees would be equivalent to, I don't know, well, five years or something. I mean, two to the -- 81 -- what's 81 times 8? Well, at any rate, it's a very long expiration date.

But, of course, you couldn't use that for labeling from the point of view of the FDA because you have to do it at actual room temperature. So you have to actually study it for -- if you want a five-year expiration date, you have to study it for five years.

But the POSA looking at this data would say this

compound is very stable at 1 milligram per mL.

Q. And with respect to the 60-degree Celsius temperature, the eight-week period we see where the solution remains very stable, that corresponds roughly to the two-month period set forth in your book, correct, for assessing stability?

A. Yes, right. Yeah --

THE COURT: Two-year?

BY MR. DITTMANN:

Q. I'm sorry. The two-month period for assessing accelerated stability that we discussed, and maybe we can turn back to that in your book, the table we were looking at?

A. Yes.

THE COURT: I believe you.

THE WITNESS: Yeah. Okay. So it's very stable at two weeks. This would extrapolate to a two to -- okay, at two weeks, the stability would extrapolate to a two- to three-year shelf life, yes, because the reaction rate increases threefold for every 10 degrees. That's what's taught in the other part of the textbook.

And so between 30 and 60 degrees is ten -- three times three times three, that's what, three times nine -- 27, that's what, 81? So 81 times two weeks, that's 160 weeks? 162 weeks? How many -- that's -- what? Three years.

So it's a two to three -- this, I mean, that's an extremely rough calculation, but this would extrapolate to a

two- to three-year shelf life. That's an extrapolation. It wouldn't be believed -- I mean, because it's like -- okay, a POSA looking at this would say, we're in pretty good shape, from the point --

THE COURT: It's an indication?

THE WITNESS: Yes, yes, yes.

BY MR. DITTMANN:

Q. Do the preformulation data concerning this 1-milligram-per-milliliter solution support your opinion that a POSA would not want to add any excipients like a chelating agent?

A. Yeah, absolutely, yes.

Q. Is this because of the principle we discussed earlier, the golden rule that you don't add excipients unless absolutely necessary for I.V. solutions?

A. Yes, correct, yes.

Q. And do you understand that plaintiffs' clinical expert, Dr. Keith Candiotti, testified as to the palonosetron concentrations that would be preferred from a clinical perspective?

A. Based on the prior art, yes, I understand, yes, sir.

Q. And using Dr. Candiotti's most preferred 1 to 2 milliliter volume that you mentioned earlier, this would include a 1-milligram-per-milliliter concentration for a 2-milligram dose, correct?

A. In a 2 mL injectable vial, yes.
Q. Based on the 1-milligram-per-milliliter data we see here, would there be any stability-related reason to want to use lower concentrations of palonosetron?
A. No, no. I mean, it's out of the clinical range, the expected clinical range, and your concentration of a milligram per mL is stable, so there's no reason to go to lower concentrations.
Q. Now, as we saw earlier, the claims that you've analyzed in the case, they specify 0.05 milligrams per milliliter palonosetron concentration, correct?
A. Yes. Correct.
Q. So if we can pull out of the -- zoom in here and look at the table.

And I want you now to assume, Doctor, that a POSA in this case would have wanted to focus on this 0.05 milligram per milliliter concentration. Are you with me so far?
A. You want me to assume?
Q. To assume --
A. Assume that, okay.
Q. -- just focusing now on 0.05 milligram per milliliter palonosetron concentrations.
A. Um-hum. Okay.
Q. So, with that assumption, what would the data we see here in the Bonadeo declaration, if anything, regarding the need to

add a stabilizing agent like a chelating agent?
A. Well, you can see that at the concentration of .01, .1 and 1, the compound, palonosetron, is quite stable, and particularly in this range of .05, which is in between .01 and 1. There's no -- there's no instability here. A POSA would not expect there to be any difference between instability for a .05, if that's what you're asking. So there's no stability reason, even at that low concentration, to add anything to the formulation.
Q. And the .05-milligram-per-milliliter concentration would be roughly in the middle of the two --
A. Yeah, halfway in between, yeah.
Q. -- concentrations we're looking at here, 0.01 --
A. Yeah, right in between.
Q. -- and 0.1?
A. Yes.
Q. And is it correct that up until 60 degrees Celsius, there -- well, can you tell us, through 60 degrees Celsius, what, if any, degradation are we seeing for either concentration?
A. I see none. None.
THE COURT: In fact, you're coming up with one percentage point more than you started with?
THE WITNESS: Yes. That would presumably be the analytical sensitivity. Although there isn't an initial --

this is only one week. So that may be just in the initial form -- you know, they had 101 initially, that's my expectation.

THE COURT: Okay.

BY MR. DITTMANN:

Q. Can we zoom in just on the very top line what we are seeing here, the title? And do we see, Doctor, that the experiments we are discussing were performed at a pH of 7.4?

A. Yes.

Q. Does this pH level have any significance to you in interpreting the stability results we are looking at?

A. Well, okay, at first thought a POSA would say, well this -- I don't know if this is the optimal pH or not, and so what I do know from the preformulation report that this was -- 7.4 was not the most stable pH. So the most stable pH from subsequent preformulation work was pH 5.

Q. So is it correct a POSA would expect even better results in terms of stability if the solutions were maintained at the optimal pH of 5?

A. Yes, yes.

THE COURT: Before we leave this chart, I think I misunderstood. The last column there, Doctor, that has number -- that has the results at eight weeks.

THE WITNESS: The eight week one?

THE COURT: Yes.

THE WITNESS: Yes.
THE COURT: Those are milliliters, right?
THE WITNESS: No, that's -- that's percentage --
THE COURT: It is a percentage?
THE WITNESS: Percentage, yes. It is the chemical stability, so that's the percentage.
THE COURT: All right.
THE WITNESS: This says, "percent drug remaining," yeah.
THE COURT: Okay. Fine. I did understand.
THE WITNESS: Yeah, okay.
BY MR. DITTMANN:
Q. Now, could we zoom in now on the 10 milligram per milliliter data? And can you explain, Doctor, what, if anything, these results would have explained to a POSA who performed these preformulation studies?
A. Well, I think a POSA, and even myself, would look at this and say this is unusual. We're seeing here, in the extreme at 8 weeks, you can see the potency is decreasing, and then it's increasing at these very high temperatures. That means something physical, chemically, odd or funny is happening. Maybe there is some compound that's melting or there is some chemical transition you're not aware of or change in reaction mechanism. But this is saying there is some complicated non-linearity occurring here at this high concentration of 10

milligram per mL. Maybe there self-association, micellization, something complicated. And I know that the -- that you can speculate, but I don't know that it's -- we don't know what's going on there.

Q. Now, with this unusual temperature data we are looking at for the 10 milligram per milliliter solutions, have suggested to a POSA that oxidation was involved here?

A. No, no. Because this is not what -- not at all what you'd expect. High temperatures, you have more instability because you've got higher thermal energy and more vibration associated with the chemical bonding, so this is very unusual.

Q. Now, putting aside for a moment this unusual data, is it correct that palonosetron concentrations at 10 mg per milliliter and higher were found to be unstable in the preformulation experiments?

A. Yes. Correct.

Q. Can we bring up PDX-717? Can you explain what we see here, Doctor?

A. Well, here is kind of my take away from the preformulation studies, which as I said are not part of the prior art. But these are part of the confidential studies to show the uniqueness of the palonosetron compound. And first is that lower concentrations have good stability illustrated by the .01, .1, and 1 concentrations, while the concentrations of 10 milligrams per mL and higher have poor, non-linear

stability. And while we didn't show that 50 milligram, but it was similar. The 50 milligram per mL concentration, and no mechanism for oxidation or chemical instability can explain this data.

The higher concentrations of 10 milligram per mL and higher have poor non-linear stability, and no mechanism of oxidation or chemical instability can explain this data.

Q. Now, Doctor, I want you to assume for purposes of my next few questions, that a POSA was convinced that oxidation was an issue in palonosetron. Are you with me so far?

A. Okay.

Q. And I understand you disagree, but I want you to assume they were concerned about oxidation.

A. Um-hum.

Q. How many different methods would a POSA have tried in an attempt to address such an oxidation problem?

A. Well, I think there's several, many methods, and I think I illustrate that in a transparency taken from my textbook on Chemical Stability of Pharmaceuticals, and I think we have a transparency on that.

Q. Yes --

A. I think I list nine different methods.

Q. Can we bring up PDX-718, please.

A. So here I have listed from our Chemical Stability of Pharmaceuticals in the lower right handbook, and this is the

different methods. Here are things that you would do. You would purify out contaminants. That's always an objective because they can accelerate degradation, react with your API. But you can remove oxygen, you can adjust the pH, ionic strength, as well as buffer capacity. Adjust the concentration of the API, depending on the reaction mechanism. Protect it from light like put it in amber bottles or something.

THE COURT: So light has a -- has an effect on oxidation, not just on the thing that is light engendered? What's the name of that?

THE WITNESS: Okay. There is photolytic degradation and oxidation.

THE COURT: Right.

THE WITNESS: And they are two different mechanisms, yeah, yeah.

THE COURT: But light can affect oxidation?

THE WITNESS: It can -- light can affect oxidation, yes, through energizing the electrons in the molecule. And --

THE COURT: Keep going. That was Number 5.

THE WITNESS: Yeah. And so then you can change the formulation container, because glass and plastic have different permeabilities to air; oxygen in particular. So you can change the permeability. You can use a chelating agent, but if -- only if the oxidation was caused by metal ions or

catalyzed by metal ions. That's the catalysis by metal ions is key. And then you can add antioxidants or you could refrigerate. That's not preferred. And antioxidants are less preferred, but...

So, those are the various mechanisms you have to try and deal with oxidation and photolytic degradation.

Q. And as we see at the bottom of the slide, Doctor, these are some of the options that are set forth in your book?

A. Yes, yes.

Q. Chemical Stability of Pharmaceuticals?

A. Yes, yes.

Q. Now, focusing for a moment on option 4 of your demonstrative, adjusting the concentration of the API, we touched on this a little while ago with respect to the Bonadeo preformulation data, right?

A. Yes.

Q. Based on the preformulation data we looked at, would a POSA believe that using a concentration of 1 milligram per milliliter would have been sufficient to address any oxidation issue?

A. Yes. That's what the data indicates.

Q. Now, I want to focus you on option number 7 here on the screen. And based on the data you've seen, do you have an opinion as to whether a POSA considering this option would have actually tried a chelating agent?

A. You would not try a chelating agent, unless you saw a metal ion affect, and I think that was studied in the preformulation report. But you don't add a chelating agent unless you need it. And you have to have evidence that you need the chelating agent.

Q. Can we bring up PDX-719, please. And can you explain first, Doctor, what are we seeing here on this slide?

A. So here we have palonosetron with metals and palonosetron -- I'm sorry and without metals. And here looking at the concentration where you would use the temperatures that you would use for your expiration dating, you can see that there is very little or no effect of palonosetron -- of metals, with or without metals at the low concentration of .1 milligram per mL.

And so at the high concentration it's more equivocal here with or without metals. But at the low concentration, the compound appears to be stable in the presence of metals. This would imply that catalysis by metals is not a problem for the pharmaceutical stability of palonosetron.

THE COURT: And this is the Bonadeo data where the experimenters actually intentionally added the metal ions as the patent was being prosecuted in order to demonstrate that metal ion degradation wasn't likely with palonosetron.

THE WITNESS: Correct. Metal ion catalysis, correct. Yes. They added, I think, chromium, iron, and -- it's listed,

but they added a combination of metals.
Q. And again, as we see, the bottom of this slide, PDX-719, the data comes from the supplemental declaration of Daniele Bonadeo from application Number 11/388,270?
A. Yes. Correct.
Q. And it's dated June 8th, 2009?
A. Correct, yes.
THE COURT: Mr. Dittmann, did I accurately characterize what the origin of this table is?
MR. DITTMANN: Yes.
THE COURT: As far as you know?
MR. DITTMANN: Yes.
BY MR. DITTMANN:
Q. And just as a refresher, Doctor, this information was not available in the prior art, correct?
A. Correct. Right.
Q. And you were discussing this data only in response to Dr. Kirsch's testimony concerning what a POSA would have determined based on routine preformulation studies, correct?
A. Correct, yes.
Q. Now, I want to focus on the 100 degree Celsius data for the 0.1 milligram per milliliter solutions?
A. Yes. Okay.
Q. And we see that for the solutions with metals, the potency after 8 weeks was 24 percent in both instances?

A. Yes. Two samples presumably, yes.
Q. And that's in comparison to 96 and 98 percent for the same temperature in the solutions without metals, correct?
A. Yes. Correct. Yeah.
Q. Do you agree that that would show significant degradation, at least at that temperature?
A. I think these -- yes. And you would probably try to identify and purify the degradation products. But it doesn't really -- a hundred degrees is -- a POSA would not consider doing that for stability purposes. It would be the 40 and 60 degree data that you would use for extrapolating your pharmaceutical stability considerations. But, yeah.
Q. Would a POSA consider the 80 degree Celsius or 100 degree Celsius information in deciding whether to add any excipients to a palonosetron I.V. formulation?
A. No. No. Those are considered extreme conditions for other purposes. But not for expiration dating.
Q. And, again, with respect to the 60 degree Celsius and lower temperatures, we are not seeing any significant degradation when metals were included in the solutions, correct?
A. Correct. Yes. Eight weeks is a very stable product at room temperature -- at 60 degrees.
THE COURT: You are referring to the smaller quantity of samples?

MR. DITTMANN: Yes, we're referring to the 0.1 milligram per milliliter --

THE WITNESS: Yeah.

BY MR. DITTMANN:

Q. -- 60 degree Celsius?

A. Yes. This is the key data here, that a POSA would use, regarding the pharmaceutical stability of palonosetron.

Q. Will you, Doctor, briefly describe what we are seeing for the 10 milligram per milliliter solutions?

A. Well, the 10 milligram per mL, as I said, the high concentration is 10 milligram per mL and the other previous data, 50 milligram per mL has got some very complicated physical chemistry here. It's not stable here or here, even without metals, although it's very stable at a hundred degrees; this is room temperature and a hundred degrees. So this is not understandable to a POSA. So we would say ten milligrams per mL, this concentration, something funny, complicated is happening. We don't know what it is. I don't think it's known what it is today. I would look at this and say this is an interesting Ph.D. project, but that's it.

Q. Whatever interesting might be happening at the 10 milligram per milliliter solution, is it correct that this is not happening at the lower 0.1 milligram per milliliter solution?

A. Correct, yeah. So a POSA will have accomplished his job

by developing a stable pharmaceutical product.

Q. To summarize this section of your analysis, would a POSA viewing the data on PDX-719 be motivated to use a chelating agent to any attempt to improve stability?

A. No. There would be no justification for a chelating agent. Based on this data, for room temperature stability.

Q. Your Honor, we are about to shift topics, and, perhaps, if it's okay with you we can stop for the day and have maybe 45 minutes to an hour to finish tomorrow morning?

THE COURT: That will be fine. We kept going as long as we could in order to get as much of the direct on to the record today, but I think this is a good stopping point.

MR. O'MALLEY: Your Honor I wonder just so that everyone can sort of plan their day tomorrow including, perhaps, leaving town, would the defendants have any estimate of how long the cross, they might have, I'm not holding them to it, and are both defendants planning to cross Dr. Amidon?

MR. LOMBARDI: Our plan is right now I will just be doing the cross. I am very -- I have a great incentive to do this as efficiently as we can, and I -- with an hour left, it's a little bit hard for me to predict, but I'm going to say it's going to be at least an hour, and hopefully less than two but I --

THE COURT: Okay. All right. So once Dr. Amidon's testimony is complete, you have one more segment of

depositions that you're working out as best you can tonight?

MR. DITTMANN: Correct.

THE COURT: And that's about an hour's worth.

MR. DITTMANN: We are trying to see if we can come to an agreement to make it even less, but the parties are working on that, and we hope to come to an agreement tonight.

THE COURT: And then I guess we need to know what the defendants', plural, inclination is regarding rebuttal.

MR. LOMBARDI: As of right now there will be no rebuttal case, Your Honor. We should chat tonight, but as of right now, no rebuttal case.

THE COURT: Okay. And my question to you all at the end of the presentation of the evidence will be what you would like to do in the way of summation either written or oral or both and when, but I won't keep you at all once you finish the presentation of the evidence. You'll be free to pack up and go, and we will take this up further as we all mutually decide to do so.

MR. DITTMANN: If I may, Your Honor, one note just to clarify. We were informed over the weekend that there would be no rebuttal witnesses, so if there are going to be any, we certainly need to know. We were told there wouldn't be any.

MR. LOMBARDI: Well, we haven't heard -- I think we have always said what our -

THE COURT: Right.

MR. LOMBARDI: We have been in good faith, Your Honor.

THE COURT: It's clear.

MR. LOMBARDI: And we have not heard the end of their case.

MR. DITTMANN: Yes. They said in court, but that's fine.

THE COURT: Okay. See you tomorrow. Thank you all.

(The proceedings concluded at 4:36 p.m.)

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